THE RELATIVE ROLES OF PORTAL HYPERTENSION AND OF CIRRHOSIS IN THE PATHOGENESIS OF PULMONARY LESIONS ASSOCIATED WITH CHRONIC LIVER DISEASE

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To my Mother and Father

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2 ABBREVIATIONS

FRC	Functional Residual Capacity
TLC	Total Lung Capacity
FVC	Forced Vital Capacity
FEV1	Forced Expiratory Volume in 1 second
RV	Residual Volume
TLCO (sb)	Single breath Carbon Monoxide Transfer Factor
KCO	Transfer coeffient
PO2	Partial pressure of oxygen
PCO2	Partial pressure of CO2
PaO2	Partial pressure of Oxygen in arterial blood
PaCO2	Partial pressure of Carbon Dioxide in arterial blood
A-a	Alveolar arterial oxygen gradient
V/Q	Ventilation Perfusion ratio
VO2	Oxygen uptake
VCO2	Carbon dioxide production
Qs/Qt	Shunt fraction
VD/VT	Dead space to tidal volume ratio

3 SUMMARY

There have been numerous reports of cardiovascular and pulmonary abnormalities in patients with cirrhosis and portal hypertension. The role of portal hypertension in the pathogenesis of pulmonary abnormalities in patients with liver disease has not been defined. The present study was therefore undertaken to clarify this.

Pulmonary function, including exercise testing, was evaluated in two groups of patients, 11 with portal hypertension due to cirrhosis and 10 with extrahepatic portal vein thrombosis and normal liver histology. Carbon monoxide gas transfer (TLCOsb) was less than 75% of predicted values in four patients from each group. One patient from each group had clinical and catheter confirmed evidence of pulmonary hypertension. Abnormal cardiorespiratory responses to exercise occurred in three patients in the extrahepatic group. Two had associated low TLCOsb and one developed arterial desaturation on exercise. A similar pattern was seen in three patients with cirrhosis. All had low TLCOsb and one developed arterial desaturation during exercise. In the cirrhotic group however three additional patients showed reduction in PaO2 unassociated with elevated heart rate response on exercise. There was no significant

correlation with the presence of autoimmune antibodies which appear to be a secondary phenomenon.

Our results suggest that pulmonary hypertension is linked to the presence of portal hypertension. Reduction in arterial PO2, appears to occur only in patients with liver disease, presumably on the basis of intrapulmonary shunting.

4 INTRODUCTION - Pulmonary Abnormalities in Liver Disease

In 1884 Fluchliger described a cirrhotic patient with cyanosis and clubbing and no apparent cardiovascular or respiratory disease. Since this original description certain pulmonary abnormalities have been well documented and in addition certain cardiovascular effects have been observed including tachycardia, increased aortic blood flow, widened pulse pressure, expanded blood volume, reduced vascular resistance and shortened circulation time (1). The pulmonary abnormalities are:

4.1 Arterial hypoxaemia

Arterial desaturation was initially thought to be due to a shift to the right of the oxygen dissociation curve as demonstrated by Snell and Keys (1) in vitro. It appears however, in vivo, that while there may some minor shift of the curve it contributes little, if at all, to the observed desaturation. Anaemia has also been suggested to contribute but abnormalities of reaction rate between oxygen and haemoglobin, and the functional impairment of the erythrocyte have so far not been adequately studied. In addition while these may explain a degree of desaturation they do not readily explain a reduction in PaO2.

Restriction of chest wall movement and lung volumes by tense ascites cannot be the explanation as desaturation is observed in the absence of ascites. Ruff et al (4) using 133Xe demonstrated increased closing volumes in 10 seated cirrhotic patients and in 8 of these it was greater than the FRC. They concluded that the V/Q ratio of the dependent lung zones may be very low primarily as a result of decreased ventilation due to airway closure. They postulated this may be due to mechanical compression of small airways by dilated blood vessels and/or interstitial pulmonary oedema. Other studies have shown normal closing volumes and Schomerus (13) demonstrated no inequality as judged by nitrogen washout. In addition over half the patients who were studied were smokers. In his study of cirrhotic patients Schomerus (13) found reduced diffusing capacity to be an important contributing factor to the desaturation. While low carbon monoxide and oxygen diffusion have been shown to occur in cirrhotic patients the reasons for this are not clear. Apart from the occasional case of fibrosing alveolitis associated with chronic active hepatitis the degree of alveolar membrane damage is not sufficient to account for the measured abnormalities and regional ventilation abnormalities have not been consistently demonstrated(13,14). While true shunting can occur through portopulmonary channels, intrapulmonary vascular malformations or through spider naevi on the pleural surfaces the magnitude of anatomic shunts demonstrated has not correlated with the degree of desaturation

observed(15,16). It has also been pointed out that because of the high oxygen tension in portal blood, it would require massive porto-pulmonary shunting to affect arterial saturation significantly.

The most attractive explanation follows from the demonstration of intrapulmonary shunting by various techniques including systemic scanning following the injection of radioactive macroaggregated albumin.(16,17,18) Dilated gas exchanging vessels are thought to result in reduced transit time and increased diffusion distance to central erythrocytes. In this way the end pulmonary capillary blood is prevented from reaching equilibrium with alveolar oxygen tension. The degree of desaturation has been shown to have some correlation with liver function in the individual patient and it has been suggested that this is a hepatopulmonary syndrome analagous to the well known hepatorenal syndrome(19). Why the intrapulmonary vascular channels should be dilated is uncertain. It may result from an endogenous vasoactive product which is normally metabolised by the liver, although the nature of this substance is unknown. Daoud (20) has demonstrated loss of pulmonary vasoconstrictor response in cirrhotic patients but Naejie (21) who was unable to confirm this observation speculates that Daoud's patients may have had endotoxaemia.

4.2 Pulmonary Hypertension

Mantz and Craig noted the occurrence of pulmonary hypertension and portal hypertension thirty years ago and this observation has been subsequently confirmed. Lebrec et al (3) reported 9 patients with pulmonary hypertension complicating portal hypertension. The cause of the portal hypertension was cirrhosis in 7 patients, nodular regenerative hyperplasia of the liver in 1 and portal vein obstruction in 1. They postulated that pulmonary hypertension might result from the effect of a vasoconstrictive agent or substance toxic to the pulmonary arterial walls, which is produced in the splanchnic territory and normally destroyed by the liver.

A recent large study by Mcdonnel et al (4) would appear to exclude a coincidental association. They found a prevalence of primary pulmonary hypertension in an unselected series of 17901 autopsies of 0.13% in all patients but 0.73% among patients with cirrhosis ($p<0.001$). A clinical series of 249 patients with biopsy proven cirrhosis showed a prevalence of 0.61% which is also significant ($p<0.001$) compared to the autopsy series. However, the description of pulmonary hypertension in patients with portal vein thrombosis and normal liver histology (5) suggests that this pulmonary hypertension may be due to impeded portal venous blood flow and not to hepatic dysfunction.

4.3 Respiratory Alkalosis

Hyperventilation and respiratory alkalosis are frequently observed in cirrhotic patients, particularly those who are encephalopathic. The exact mechanism of this disorder is unknown. The decrease in arterial oxygen saturation observed is insufficient to account for the hyperventilation. Other possible mechanisms have been suggested. Progesterone has been shown to be a respiratory stimulant and is thought to be responsible for the hyperventilation of pregnancy. Progesterone is broken down by the liver and increased levels of this hormone have been postulated to be responsible for hyperventilation in cirrhotic patients.

Ammonia has also been implicated. Levels of ammonia have not been consistently correlated with the degree of hyperventilation. This has been ascribed to secondary effects of hydrogen ion concentration on the dissociation of ammonium. NH_4 is poorly diffusable but in the presence of extracellular alkalosis forms ammonia (NH_3) which rapidly enters cells and may stimulate ventilation out of proportion to its extracellular concentration. Karetzky (24) et al measured the ventilatory response to CO_2 in 7 subjects and found it to be significantly augmented in the range 30-40 mmHg, suggesting diminished tolerance to CO_2. This they suggest is compatible with a state of intracellular acidosis consequent on a low energy state of the

cells with an inability to actively extrude hydrogen ions.

Mulhausen et al (25) investigated the acid base status of 91 patients with cirrhosis. They found that although respiratory alkalosis was frequently present, this was not a pathognomonic disturbance. All varieties of acid base disturbance were observed but the common denominator was the reduction in the partial pressure of CO2. They also found that in each instance of reduced bicarbonate concentration, most of the deficit could be accounted for by elevated levels of lactate and pyruvate. The pH depended on the severity of the existing bicarbonate deficit in the presence of reduced pCO2. No correlation was found between acid base and mental status.

4.4 Pulmonary Oedema

The incidence of pulmonary oedema in patients with fulminant hepatic failure is high. In a series of 100 patients Trewby et al (26) found 37 with clinical and radiological evidence of pulmonary oedema. These patients had no clinical evidence of left heart failure and the pulmonary capillary wedge pressure measured in 12 of them was normal. There was no evidence to incriminate renal failure, endotoxaemia or hypoalbuminaemia. There was however a significantly high incidence of pulmonary oedema in patients with cerebral oedema suggesting either a

central origin for the pulmonary oedema or common factors predisposing to oedema in both sites.

4.5 Chest Radiograph Abnormalities

The presence of chest radiographic abnormalities in cirrhotics not explained by infection, fluid overload etc has been investigated by Stanley and Woodgate (21). The shadows are usually nodular, occurring at the bases, and are felt to be due to dilated intrapulmonary vessels. Radiographic shadowing appears to vary with the severity of liver dysfunction.

4.6 Aim of the study

While, as noted above, there have been reports of pulmonary hypertension in patients with extrahepatic portal hypertension, the arterial oxygen desaturation does not appear to occur in this group. This however has not previously been systematically studied. The aim of this study was therefore to clarify the relationship between these two pulmonary abnormalities and liver disease by studying lung function and exercise responses in two groups of patients; patients with extrahepatic portal hypertension with normal liver function and patients with portal hypertension due to cirrhosis.

Reports of pulmonary hypertension occurring in patients with chronic active hepatitis have suggested that this may be a manifestation of an auto-immune process. Measurements were therefore made of autoimmune markers to try and establish if these reflected paraphenomena rather than being of aetiological importance.

5 PATIENTS

The study had the approval of the ethics committee of the

University of Cape Town and Groote Schuur Hospital and all patients gave informed consent. All patients with well documented portal hypertension who were contactable, and able and prepared to participate were considered for the study. The majority of patients had initially presented with variceal bleeding and had had various radiological investigations including catheter studies and liver biopsies performed by their own physicians prior to their admission into this study. Patients were excluded from analysis if they were unable to perform exercise tests or had evidence of significant unrelated cardiovascular or pulmonary disease. Those with liver disease were studied when clinically stable and none of the patients were encephalopathic. Patients undergoing variceal sclerotherapy were not studied within a week of the procedure.

6 METHODS

Symptoms were recorded using the American Thoracic Society Respiratory Questionnaire,(6) modified to include data relating to liver disease and portal hypertension. Chest radiographs and electrocardiographs were obtained for each patient.

Lung functions included full lung volumes, flow volume loop, single breath diffusing capacity for carbon monoxide, closing

volumes and measurement of maximal inspiratory and expiratory pressures. Schonbergs(7) predicted values were used for flow volume and spirometric data, Grimby's (8) for lung volumes and Buist's (9) for closing volumes. Normal values for TLCOsb were taken from Cotes (10) and those for maximum inspiratory and expiratory pressures from Wilson.(11)

Liver function was assessed by measurement of prothrombin index, serum albumin and hepatic enzymes. Liver histology was available for each patient. In addition Rheumatoid factor, anti-DNA antibodies, antinuclear factor, antismooth muscle antibodies, antimitochondrial antibodies and circulating immune complexes were determined in each case.

Exercise testing was performed using the Jones protocol with a cycle ergometer (12). End tidal PCO2, inspired minute ventilation, heart rate, blood pressure, and arterial oxygen saturation (ear oximetry) were measured during progressive testing to exhaustion (stage 1). A 12 lead ECG was run and FEV1 and FVC were measured before and after exercise.

Steady state measurements were taken at rest and at approximately 60% of maximum workload as determined by the stage 1 test. Blood gasses were measured by means of arterialised capillary earlobe blood and cardiac output estimated by the CO2 Fick method following a rebreathing manouevre. Measurements were made of end-tidal fractional CO2 and mixed expired CO2 and O2

fractions. Standard equations were used to calculate oxygen consumption, carbon dioxide production, alveolar arterial oxygen tension gradients, shunt fraction and dead space to tidal volume ratio (12).

In addition Swan Ganz right heart catheterisation was performed in two patients with clinically significant pulmonary hypertension.

7 EQUIPMENT

Lung function was measured with computerised and manual systems. The computerised system was a Morgan Model C dry rolling seal spirometer interfaced with a Tektronix 4052 microcomputer. The Morgan Transfer test apparatus was used for single breath TLCOsb and results were corrected for haemoglobin. Closing volumes were measured with a single breath nitrogen washout technique using a HP47302A Nitrogen analyser and the dry rolling seal spirometer. A Medscience 570 Wedge Spirometer was used for Flow Volume loops and lung volume subdivisions were measured by Helium dilution with a Godart Expirograph. A Siemens Elema electrically braked cycle ergometer RE820 was used for the exercise tests. Ventilation was measured with a Parkinson Cowan dry gas meter; gas analysis was by Applied Electrochemistry S3A

Oxygen analyser and a Morgan 901 Mk2 CO2 analyser; and ear oxygen saturation by Hewlett Packard 4201A ear oximeter all linked to a Siemens Elema Mingograf 82 chart recorder. Analyses were calibrated with reference gases analysed by the Lloyd-Haldane technique. Blood gases were measured on a Radiometer ABL3 blood gas analyser.

8 RESULTS

8.1 Clinical Features.

Patients with cirrhosis were generally older and smoked more than those with portal vein thrombosis. The male to female ratio was also different, there being more males in the liver disease group. (Table 1.) None of the subjects had symptoms of asthma or atopy and none reported daily sputum production. Nine subjects felt that they were more dyspnoeic on effort than other people of their age although only two described effort limitation class 2 NYHA or greater. Both of these subjects had clinical, radiological and electrocardiographic evidence of pulmonary hypertension. One had portal vein thrombosis (patient 9) and the other chronic active hepatitis with cirrhosis (patient 21). None

of the patients were cyanosed at rest and only 1 had finger clubbing (patient 20)

Patient No	Age	Sex	Diagnosis	Splenectomy	Pack Yrs	Last smoked
1	26	Female	Portal Vein Thrombosis	No	0	NA
2	17	Female	Portal Vein Thrombosis	No	0	NA
3	19	Female	Portal Vein Thrombosis	No	0	NA
4	17	Male	Portal Vein Thrombosis	No	0	NA
5	32	Male	Portal Vein Thrombosis	No	3	7 Years ago
6	25	Female	Portal Vein Thrombosis	Yes	0	NA
7	18	Female	Portal Vein Thrombosis	No	0	NA
8	20	Male	Portal Vein Thrombosis	No	0	NA
9*	31	Female	Portal Vein Thrombosis	No	0	NA
10	24	Male	Portal Vein Thrombosis	Yes	1	Current
Mean	23.8					
M:F	4:6					

Patient No	Age	Sex	Diagnosis	Splenectomy	Pack Yrs	Last smoked
11	33	Female	Macronodular Cirrhosis	No	0	NA
12	49	Male	Alcoholic Cirrhosis	No	50	14 yrs.ago
13	27	Male	Scleros.Chol Cirrhosis	No	0	NA
14	37	Male	Alcoholic Cirrhosis	No	20	Current
15	44	Female	Chronic Active Hepatitis	No	0	NA
16	22	Male	Post Hep. Cirrhosis	No	0	NA
17	22	Male	Post Hep. Cirrhosis	No	0	NA
18	37	Male	Alcoholic Cirrhosis	No	20	Current
19	43	Female	Alcoholic Cirrhosis	No	12	Current
20	49	Male	Alcoholic Cirrhosis	No	30	Current
21*	37	Female	Chronic Active Hepatitis	No	25	Current
Mean	36.7					
M:F	7:4					

Table 1 Clinical data

* clinical and catheter confirmed pulmonary hypertension

8.2 Chest Radiographs.

These were evaluated for evidence of pulmonary hypertension and parenchymal abnormalities. Only the two patients with clinical pulmonary hypertension had radiographs clearly supporting this diagnosis. Other unrelated abnormalities noted included calcified foci in keeping with healed (probably tuberculous) granulomas, elevated hemi-diaphragm in 1 patient and minor upper lobe shadows suggestive of previous tuberculosis in 1 patient.

8.3 Electrocardiogram

These were normal in 14 patients. Patients 17 & 18 had right bundle branch block, patient 8 ectopic atrial pacemaker with intraventricular conduction delay, patient 9 severe right ventricular hypertrophy and patient 21 right axis deviation. patients 12 & 14 had non specific anterior T wave changes.

8.4 Ventilatory function.

The lung volumes and flow rates expressed as a percentage of predicted were not significantly different in the two groups and all were within the normal range. (table 2.) There was no

significant abnormality of Maximal inspiratory or Expiratory pressures or closing volumes as measured by Nitrogen washout. The only significant abnormality of lung function was reduction in the TLCOsb. This was equal to or less than 75% predicted (after correction for haemoglobin) in 4 patients with portal vein thrombosis (3,4,5,9) and in 5 patients with liver disease. (11,14 19,20,21).

8.5 Serology and biochemistry.

Liver function was well preserved in both groups. Of the cirrhotic patients only one was hypoalbuminaemic (patient 17) and 2 had low prothrombin indices. Minor elevations of circulating immune complexes and rheumatoid factor were noted in some patients as can be seen in table 3. These are felt to be secondary phenomena as none of the patients had other evidence of collagen vascular disease.

Patient No	FVC	FEV1	FEV1/FVC	TLC	TLCO
1	98	92	79	101	88
2	110	96	78	98	98
3	102	100	84	111	64
4	84	82	88	91	74
5	97	85	70	101	65
6	115	112	83	134	92
7	93	88	83	103	100
8	123	115	78	112	103
9	105	112	86	120	56
10	113	118	84	106	79
Mean	104	100	81.3	107.7	81.9
+- SD	11.59	13.37	5.18	12.29	16.7

Patient No	FVC	FEV1	FEV1/FVC	TLC	TLCO
11	87	90	86	102	75
12	110	103	72	106	76
13	100	82	66	94	77
14	112	116	78	120	64
15	118	125	84	107	105
16	96	90	80	93	78
17	127	120	84	116	94
18	93	104	89	98	128
19	90	96	86	108	69
20	105	100	81	92	71
21	105	102	78	100	57
Mean	103.9	102	80.3	103.2	81.2
+- SD	12.3	13.3	6.7	9.1	20.3

Table 2. Lung function tests expressed as a % of predicted values.

Patient no	PI	Albumin	Bilirubin	Latex	Anti DNA	Imm.Compl.
1	75	38	7	0	2	5
2	75	46	15	0	8	3
3	100	42	19	0	10	3
4	86	39	20	0	6	3
5	74	43	10	0	0	0
6	76	41	5	0	3	6
7	74	35	18	0	8	11
8	77	44	41	0	6	9
9	90	29	4	160	0	38
10	86	47	10	0	0	0
Mean	80.1	40.2	15		4.7	7.8
+-SD	9.9	5.2	10.5		3.8	10.6

Patient no	PI	Albumin	Bilirubin	Latex	Anti DNA	Imm.Compl.
11	78	38	21	0	9	8
12	80	44	24	0	0	3
13	82	39	17	0	24	5
14	68	39	14	0	4	6
15	90	41	12	0	12	18
16	60	42	15	0	8	8
17	77	34	19	0	3	0
18	71	39	44	640	4	4
19	77	40	11	0	1	0
20	75	38	14	0	0	0
21	88	43	34	0	0	0
Mean	76.8	39.9	20.4		5.6	4.8
+-SD	9.0	2.8	10.7		7.5	5.4
Normal	100	>35	<17		<7	<5

Table 3 Biochemical and serological data.

8.6 Exercise Tests

Tables 4 & 5

8.6.1 Extrahepatic group

Progressive exercise tests were considered submaximal in 3 of the patients. The most striking feature was the markedly exaggerated heart rate response observed in 3 patients (2,3, and 9). These three patients also had marked hyperventilation with arterial PaCO2 below 35mm/Hg at rest and on exercise. Two also had a low TLCOsb (subjects 3 and 9). Representative cardiac and ventilation response graphs are shown in figure 1a + b. One patient (patient 9) had clinical evidence of pulmonary hypertension. This was confirmed with pulmonary artery catheterisation which showed pulmonary artery pressures approaching systemic values on exercise. Patients 3 & 9 showed a rise in PaCO2 and dead space/tidal volume ratio on exercise. The tachycardia and limited stroke volume in the three subjects was confirmed on steady state testing. Two other patients (4,5) had moderately elevated heart rate responses which were associated with alveolar hyperventilation and development of mild metabolic .

8.6.2 Liver disease group

Progressive exercise tests were considered submaximal in 6 patients. Markedly elevated heart rate responses were seen in three patients (11,19 & 21). All three had low TLCOsb. Subject 21 had clinical pulmonary hypertension and pulmonary artery catheterisation confirmed severe pulmonary hypertension. Three other subjects (14,18 and 20) developed widened alveolar arterial oxygen tension gradients and a fall in arterial PaO2 on exercise unassociated with elevated HR response (fig 1c). In subject 20 this was associated with the development of metabolic acidosis. Subjects 14 & 20 had reduced TLCOsb.

Patient No	Age	%Pred TLCO	% Work	Max	H.R Res	V.E Res	B.P Res	Break Away
1	26	88	55	No	Normal	High	Normal	No
2	17	98	36	No	High	High	Normal	No
3	21	64	60	Yes	High	High	Low	Yes
4	17	74	90	Yes	Sl.Hi	Normal	Normal	Yes
5	32	65	90	Yes	Sl.Hi	High	Normal	Yes
6	25	92	87	Yes	Normal	Normal	Normal	Yes
7	18	100	60	No	Normal	Normal	Normal	No
8	20	103	78	Yes	Normal	Chaotic	Normal	Yes
9	31	56	43	Yes	High	High	Low	Yes
10	24	79	81	Yes	Normal	Normal	Normal	No

Patient No	Age	%Pred TLCO	% Work	Max	H.R Res	V.E Res	B.P Res	Break Away
11	33	75	53	Yes	High	High	Normal	Yes
12	49	76	80	Yes	Sl.Hi	Normal	Normal	Yes
13	27	77	60	No	Normal	High	Normal	Yes
14	14	64	65	Yes	Normal	High	Normal	Yes
15	44	105	70	Yes	Sl.Hi	High	Normal	No
16	22	78	42	No	Normal	Normal	Normal	Yes
17	22	94	50	No	Normal	Normal	Normal	No
18	37	128	44	No	Normal	High	Normal	Yes
19	43	69	40	No	High	Normal	Normal	No
20	49	71	95	Yes	Low	Normal	Normal	No
21	37	57	60	No	High	High	Normal	Yes

Table 4. Single breath Carbon Monoxide gas transfer and Stage 1 Exercise test results.
%Pred TLCO = % of predicted TLCO
% Work = % of predicted maximum workload the patient completed.
H.R. Res = Heart Rate response
V.E Res = Ventilatory response
B.P Res = Blood Pressure response
Break away = Presence of terminal breakaway response of ventilation

	Workload	VO2 ml.kg	R	PaCo2 mmHg	PaO2 mmHg	A-a	VD/VT	HR	pH
1	0	4.40	.78	22	116	5	34	64	7.58
	300	17.30	.93	34	110	2	20	125	7.38
2	0	4.80	.75	31	105	3	21	96	7.42
	200	16.10	.94	29	105	13	15	160	7.38
3	0	5.20	.66	30	91	17	27	88	7.42
	300	21.60	.83	34	85	26	29	170	7.39
4	0	5.70	.94	39	90	17	28	92	7.39
	400	23.20	.91	32	87	26	10	170	7.35
5	0	5.20	.98	34	107	8	28	75	7.44
	600	26.10	.87	27	84	36	8	156	7.36
6	0	6.40	.78	37	97	6	31	90	7.41
	400	28.80	1.02	35	99	15	15	160	7.38
7	0	4.30	.72	36	90	13	26	75	7.39
	400	22.80	.91	32	101	15	9	143	7.39
8	0	4.60	1.21	28	111	14	33	94	7.53
	700	27.00	1.08	32	102	17	7	140	7.42
9 *	0	4.50	.76	28	91	23	20	86	7.43
	100	16.90	.87	32	77	37	32	150	7.39
10	0	5.00	.87	26	101	20	23	88	7.54
!	500	28.60	.75	34	0	0	10	120	7.41
Mean	a)	5.0	.84	31.1	99.9	12.6	27.1	84.8	7.45
+-SD		.6	.16	5.3	9.6	6.8	4.7	10.1	
	b)	22.8	.91	32.2	94.4	20.7	15.5	149.4	7.38
		4.8		2.4	11.3	11.4	8.8	17.3	

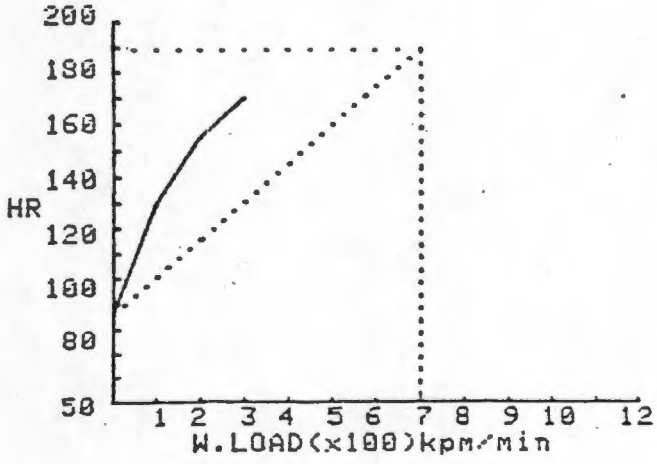
Table 5 Exercise data in patients with extrahepatic portal hypertension
* Clinical pulmonary hypertension
! 0 = unreliable data

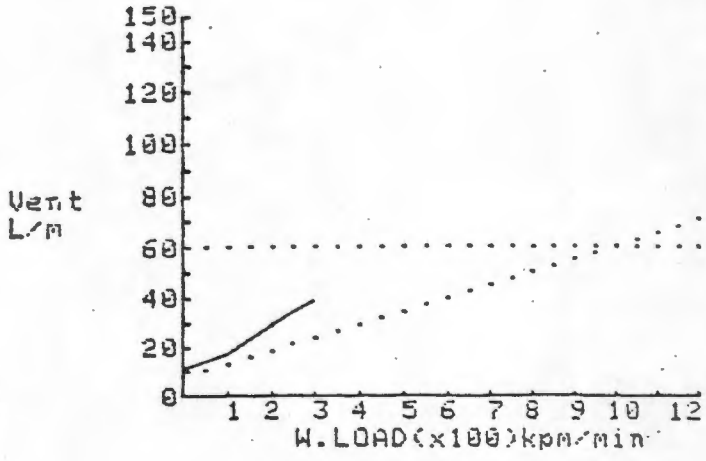
	Workload	VO2 ml.kg	R	PaCo2 mmHg	PaO2 mmHg	A-a	VD/VT	HR	pH
11	0	4.90	.76	33	95	13	31	87	7.42
	300	16.90	.98	28	104	16	14	170	7.34
12	0	3.70	.73	33	90	14	30	92	7.42
	500	15.20	1.09	38	90	22	18	147	7.38
13	0	3.10	1.11	32	101	19	19	60	7.45
	450	16.30	1.19	31	110	13	5	125	7.39
14	0	3.60	.80	30	73	40	33	78	7.43
	500	17.10	.93	26	61	60	27	113	7.41
15	0	3.90	.74	35	93	12	34	81	7.42
	300	17.30	.80	31	98	15	21	129	7.41
16	0	5.60	.86	36	90	18	31	90	7.41
	300	15.00	.88	35	91	18	20	124	7.37
17	0	4.30	.76	37	93	11	34	98	7.43
	250	18.80	.97	35	101	13	16	127	7.41
18	0	4.60	.73	33	98	8	30	72	7.45
	350	10.80	1.01	35	88	26	24	98	7.39
19	0	3.20	.80	38	83	21	35	110	7.40
	150	14.50	.70	40	81	14	28	140	7.39
20	0	5.70	.77	39	105	0	37	56	7.41
	450	24.60	.71	40	80	16	40	144	7.26
21*	0	3.70	.70	34	83	20	33	86	7.45
	200	10.40	.84	30	76	38	25	113	7.46
Mean	a)	4.2	.79	34.5	91.2	17.6	31.5	82.7	7.42
+-SD		.9	.11	2.7	9.0	8.9	4.6	15.8	
	b)	16.0	.91	33.5	89	22.8	21.6	130.0	7.38
		3.8	.15	4.7	14.1	14.3	8.9	19.6	

Table 5 Exercise data in patients with liver disease and portal hypertension
* clinical pulmonary hypertension

FIG 1

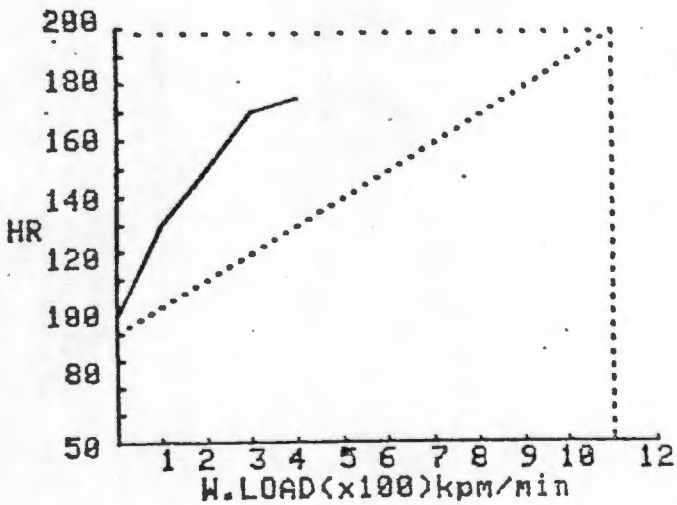
a)

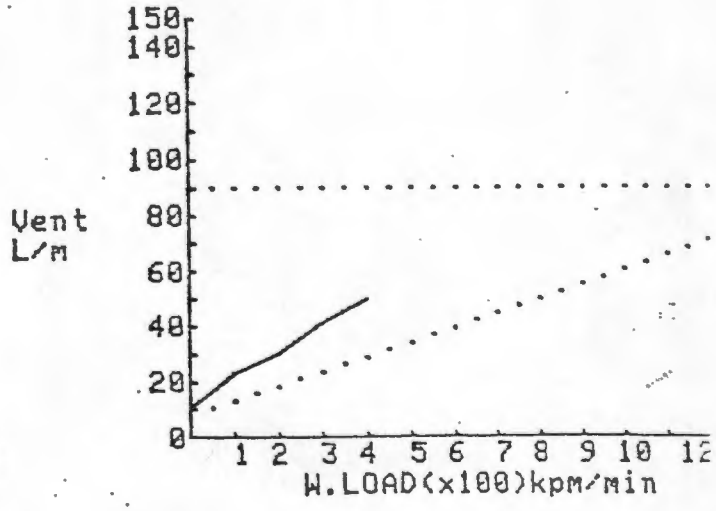




Patient 9: Extra hepatic portal hypertension with pulmonary hypertension confirmed on PA catheter.

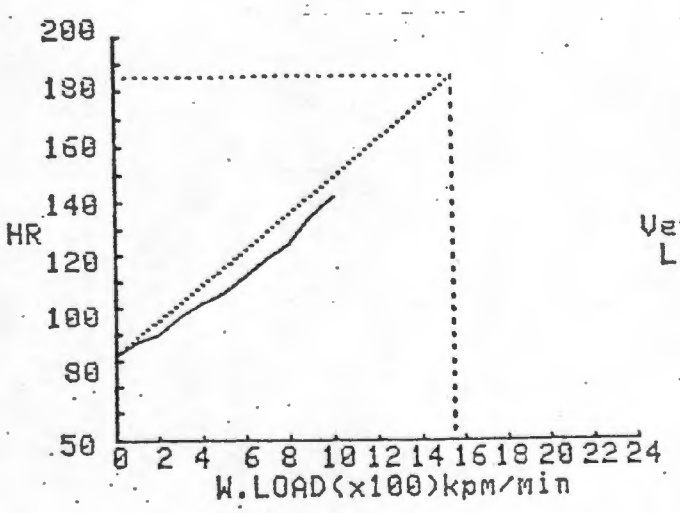
b)

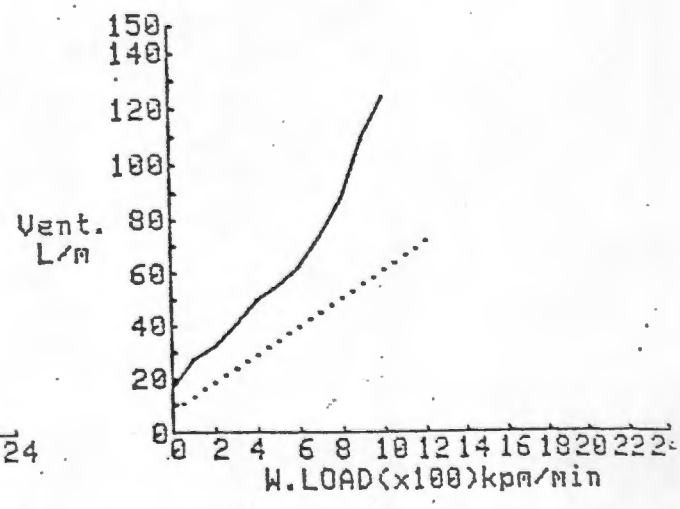




Patient 2 Extra hepatic portal hypertension

c)





Patient 14 Cirrhosis desturation without elevated Heart Rate response.

9 DISCUSSION

Pulmonary abnormalities, including arterial hypoxaemia and an increased incidence of plexogenic pulmonary hypertension, are well documented features of chronic liver disease (1-3). Most reports have attributed the plexogenic pulmonary hypertension seen in patients with liver disease to cirrhosis (3,4).

The current theories regarding the pathogenesis of arterial desaturation have been discussed (see 3.1) The fall in PaO2 on exercise in three of our cirrhotic patients with normal cardiovascular responses (14,18 & 20) could not be explained on the basis of independent lung disease.

While it is true that a number of subjects in the liver disease group were smokers, the absence of sputum production, normal chest radiographs and the presence of normal lung volumes and flow rates excludes, we believe, smoking as a cause of the reduced TLCOsb or the desaturation. As noted (section 4), patients considered to have unrelated cardiovascular or pulmonary disease were excluded from the study. Of the four subjects with reduced carbon monoxide gas transfer (14,19,20 & 21) a fall in PaO2 was only evident on exercise in two (14 & 20). The desaturation may be due to an endogenous vasoactive

product, the nature of which is unknown, but which would normally be metabolised by the liver. Our patients with liver disease were clinically well, not encephalopathic, and as evidenced by the prothrombin indices and albumin levels, had relatively good liver functions. This may well explain why we observed hypoxaemia on exercise in only a small number of patients.

The absence of desaturation in all but one of the patients with extrahepatic portal hypertension (in whom this could be accounted for by her proven pulmonary hypertension) supports the concept that defective oxygenation is related to liver disease per se and not to portal hypertension.

While the presence or absence of desaturation can easily be determined, it is more difficult to diagnose pulmonary hypertension without right heart catheterisation. In mild or early pulmonary hypertension the physiological abnormalities demonstrable by non-invasive means are non-specific. While acknowledging these limitations, the abnormal cardiovascular responses to exercise coupled with the low TLCOsb observed in the extrahepatic group strongly suggests pulmonary vascular disease. The tachycardia present in three patients was more marked than would be expected from unfitness alone and these patients were all young and active. These responses contrasted with a group of the cirrhotic patients who though older and more likely to have been physically unfit dropped their arterial PaO2 while showing normal cardiovascular response to exercise. Two of the three patients with markedly abnormal heart rate responses also

demonstrated a low TLCOsb.

Reduced TLCOsb observed in four of our patients has not previously been described in patients with extrahepatic portal hypertension in the absence of pulmonary hypertension.

Our study shows that abnormal cardiovascular responses to exercise are not uncommon and we suggest these may be related to abnormalities in the pulmonary vasculature. A transient rise in pulmonary pressures can occur during sclerotherapy which most of our patients received (22). However the two patients with severe pulmonary hypertension (9 & 21) did not have sclerotherapy and long term evaluation of the effects of sclerotherapy on the pulmonary vasculature is not available.

Of interest is that in both patients with confirmed pulmonary hypertension the liver disease or portal hypertension had been diagnosed more than 15 years earlier. This was considerably longer than the other patients in the study and would again support the concept of a long standing insult to the pulmonary circulation as the cause of the pulmonary hypertension.

Our study suggests that pulmonary hypertension may develop in response to portal hypertension, whether hepatic or extrahepatic in origin and that the pulmonary response relates to the duration of portal hypertension. Conversely hypoxaemia occurs predominantly in patients with impaired liver function and may only be evidenced on exercise in some patients. These two effects appear to be independent. Indeed the pathophysiology is completely different, the

one resulting in apparently reversible pulmonary artery vasodilatation and the other in progressive irreversible obliteration of the pulmonary vascular bed.

One can only speculate on the basis of the available published reports and experimental data as to what determines the development of the vascular changes. The two abnormalities have not been described occurring together and they would appear conceptually to be mutually exclusive. This study supports the concept of longstanding portal hypertension being linked to the development of pulmonary hypertension. Arterial desaturation appears to occur only in the presence of liver dysfunction and seems to reflect dynamic vascular changes which can occur more acutely and show varying degrees of severity in the same patient. The patients selected by having developed obliterative vascular changes would be incapable of significant pulmonary vasodilatation. Conversely the patients with vasodilatation as a result of severe liver disease may either have their survival limited by the liver disease before they can develop pulmonary hypertension or possibly are protected by the vasodilatation.

The pathogenesis of plexogenic pulmonary hypertension remains obscure (27). Its occurrence in the setting of portal hypertension is used as evidence that it results from endothelial injury. Similarly, suprisingly little is known about the mechanisms of vascular control both in the pulmonary and systemic vasculature (28). Here again attention is presently focused on the role of the endothelial cell.

The patients with portal hypertension with and without cirrhosis are therefore of considerable interest as they are unique as models for these diseases. We have tried to separate the two groups and believe our findings lend support to the proposed mechanism of desaturation and pulmonary hypertension.

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11 APPENDIX 1 Detailed lung function results

Study no	Age	Sex	FVC	FVC Predicted	FEV1	FEV1 Predicted	FEV1/ FVC
1	26	Female	3220	3270	2570	2790	79%
2	17	Female	3250	2950	2550	2640	78%
3	19	Female	2560	2490	2160	2150	84%
4	17	Male	2820	3340	2490	3020	88%
5	32	Male	4710	4820	3340	3890	70%
6	25	Female	3380	2920	2800	2480	83%
7	18	Female	3170	3390	2640	2980	83%
8	20	Male	5100	4130	4000	3470	78%
9	31	Female	2350	2230	2030	1810	86%
10	24	Male	4600	4050	3900	3290	84%
11	33	Female	2830	3230	2420	2660	86%
12	49	Male	5450	4910	3950	3830	72%
13	27	Male	5250	5200	3450	4170	66%
14	37	Male	5320	4710	4170	3590	78%
15	44	Female	3900	3300	3300	2640	84%
16	22	Male	3720	3860	2990	3320	80%
17	22	Male	4400	3450	3700	3070	84%
18	37	Male	5450	5840	4850	4640	89%
19	43	Female	2650	2930	2300	2390	86%
20	49	Male	3700	3910	3000	3000	81%
21	37	Female	3860	3650	3020	2950	78%

Volumes expressed in ml.

Detailed lung function - continued

Study No	TLC	TLC Predicted	RV	RV Predicted	RV/ TLC	FRC	FRC Predicted
1	4270	4190	1250	930	29	2080	1900
2	3810	3880	770	930	20	1800	1820
3	3410	3050	930	560	27	1360	1350
4	3940	4290	1130	1030	28	2080	2020
5	6560	6450	2040	1630	31	3500	3260
6	4870	3620	1000	700	21	2110	1650
7	4440	4270	1200	880	27	2260	1850
8	5890	5250	985	1120	17	2510	2540
9	3400	2830	1080	600	31	1860	1320
10	5580	5240	1170	1190	21	2120	2580
11	4350	4230	143	990	33	2410	1940
12	7040	6600	1980	1690	28	3100	3240
13	6285	6640	1470	1440	23	3290	3190
14	7380	6100	1680	1390	23	3190	2930
15	4970	4610	1210	1310	24	2530	2190
16	4640	4940	910	1080	19	2100	2410
17	5210	4480	990	1030	19	2590	2230
18	7280	7370	2110	1530	29	3880	3410
19	4270	3920	1650	990	39	2270	1830
20	5205	5640	1860	1730	36	3680	3020
21	5030	5050	1170	1400	23	2910	3650

Volumes in ml

Detailed lung function - continued

Study No	TLCO*	TLCO Predicted	TLCO Corrected	KCO Predicted	KCO
1	17.13	26.79	23.63	4.24	5.65
2	18.80	20.00	19.74	5.20	6.00
3	15.37	25.69	16.59	5.04	5.75
4	21.51	29.02	21.51	6.20	5.70
5	21.47	34.48	22.75	3.38	5.33
6	21.00	24.90	23.10	5.30	5.70
7	22.35	23.00	23.02	5.66	5.80
8	33.14	32.20	33.47	5.89	5.80
9	10.90	24.20	13.62	3.30	5.50
10	25.00	29.70	23.75	4.60	5.60
11	18.50	25.20	19.05	5.00	5.50
12	27.00	33.80	25.92	3.90	4.70
13	26.00	35.80	27.82	5.00	5.50
14	17.90	31.00	20.04	2.62	5.10
15	26.00	24.90	26.26	5.15	5.30
16	24.70	34.50	27.17	5.10	5.70
17	19.67	23.00	21.83	4.02	5.70
18	34.90	28.00	35.94	4.90	5.10
19	15.00	22.80	15.75	5.00	5.30
20	18.14	24.70	17.77	3.80	4.70
21	15.60	27.00	15.60	3.37	5.40

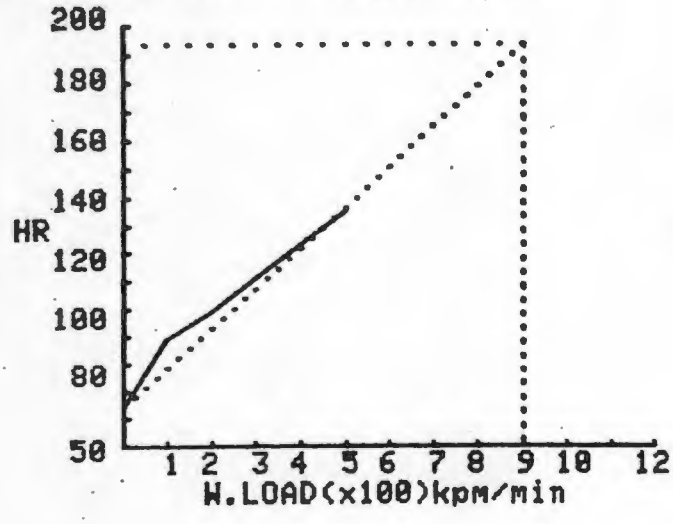
* ml/min/mmHg

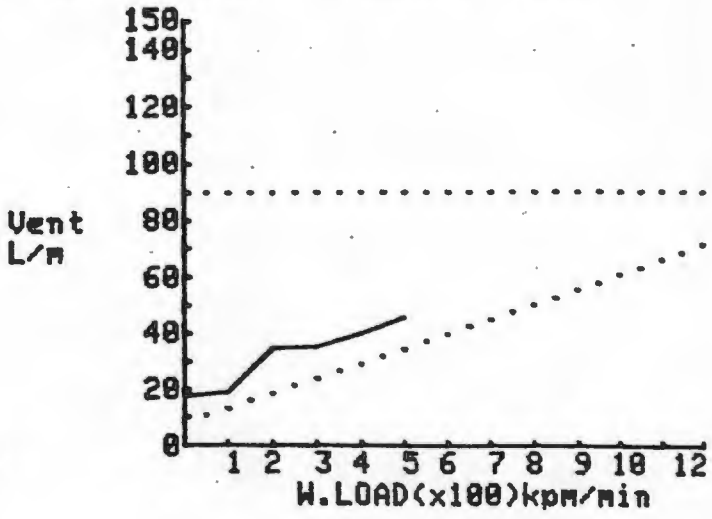
12 APPENDIX 2 Detailed Exercise Results

SPIROMETRY:

Pre-exercise: FEV1: 2530 ml FVC: 3050 ml Ratio: 82 %

Lowest post-: FEV1: 2370 ml FVC: 2890 ml Time: 5 min



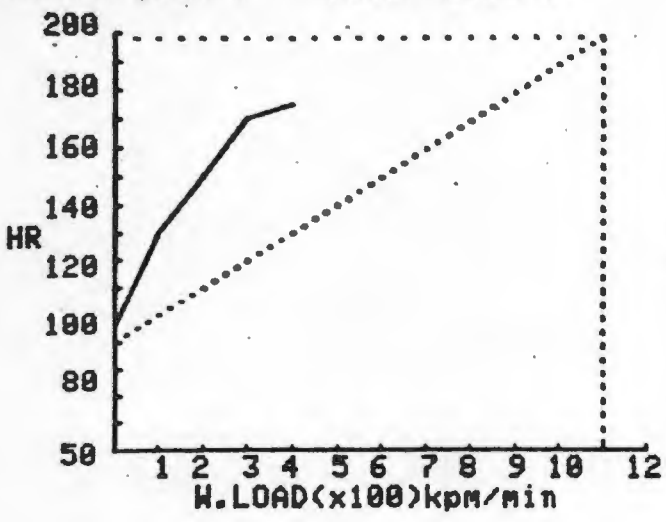


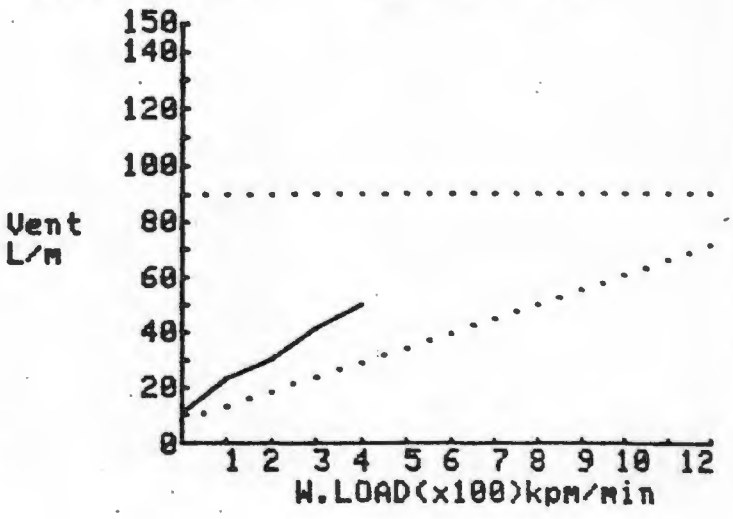
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	64	17	30	572	97	17	100	70
100	89	19	28	680	97	23		
200	99	35	60	578	97	19	110	70
300	111	35	55	638	97	23		
400	123	40	51	783	97	25	120	70
500	135	46	38	1202	96	26		

W.LOAD kpm/m	REST	300	0
HEART RATE	64	125	0
VI l/m	17	32	0
Vt ml	572	1062	0
RESP.RATE	30	30	0
VO2 ml/m	226	883	0
VO2 ml/kg/m	4.4	17.3	0.0
VCO2 ml/m	175	822	0
R	0.78	0.93	0.00
PECO2 mm	9	22	0
PETCO2 mm	17	24	0
PVCO2 mm	34	51	0

W.LOAD kpm/m	REST	300	0
PaCO2 mm	22	34	0
Vd/Vt %	34	20	0
VA l/m	11	26	0
PaO2 mm	116	110	0
SaO2 %	99	98	0
PAO2 mm	121	113	0
A-aDO2 mm	5	2	0
QS/QT %	0	0	0
QT l/m	2.6	10.1	0.0
STR.VOL ml	41	81	0
PH	7.58	7.38	0.00
LACTATE mm/l	0.0	0.0	0.0

SPIROMETRY:
Pre-exercise: FEV1: 2480 ml FVC: 2940 ml Ratio: 84 %
Lowest post-: FEV1: 2450 ml FVC: 2900 ml Time: 8 min





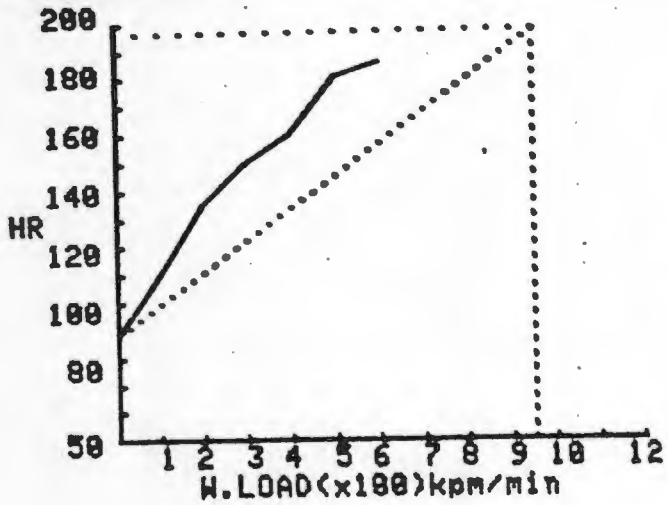
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	96	11	17	620	96	32	130	75
100	130	23	27	850	95	32	150	90
200	150	30	32	943	96	29		
300	170	42	40	1040	96	26	150	90
400	175	50	48	1043	96	25		

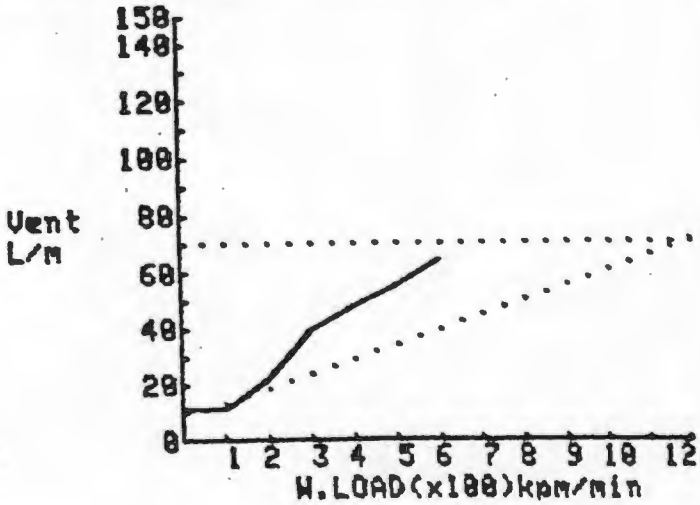
W.LOAD kpm/m	REST	200	0
HEART RATE	96	160	0
VI l/m	11	37	0
Vt ml	619	958	0
RESP.RATE	17	39	0
VO2 ml/m	274	923	0
VO2 ml/kg/m	4.8	16.1	0.0
VCO2 ml/m	205	870	0
R	0.75	0.94	0.00
PECO2 mm	17	20	0
PETCO2 mm	32	25	0
PVCO2 mm	42	52	0

W.LOAD kpm/m	REST	200	0
PaCO2 mm	31	29	0
Vd/Vt %	21	15	0
VA l/m	8	32	0
PaO2 mm	105	105	0
SaO2 %	98	98	0
PAO2 mm	109	117	0
A-aDO2 mm	3	13	0
QS/QT %	0	1	0
QT l/m	3.6	8.1	0.0
STR.VOL ml	37	50	0
PH	7.42	7.38	0.00
LACTATE mm/l	0.0	0.0	0.0

PREDICTED VALUES: FEV1: 2120 ml FVC: 2470 ml
Max.HR: 196 Max.W.Load: 950 kpm/min Max.Vent: 70 L/min

SPIROMETRY:
Pre-exercise: FEV1: 1910 ml FVC: 2350 ml Ratio: 81 %
Lowest post-: FEV1: 1960 ml FVC: 2370 ml Time: 5 min





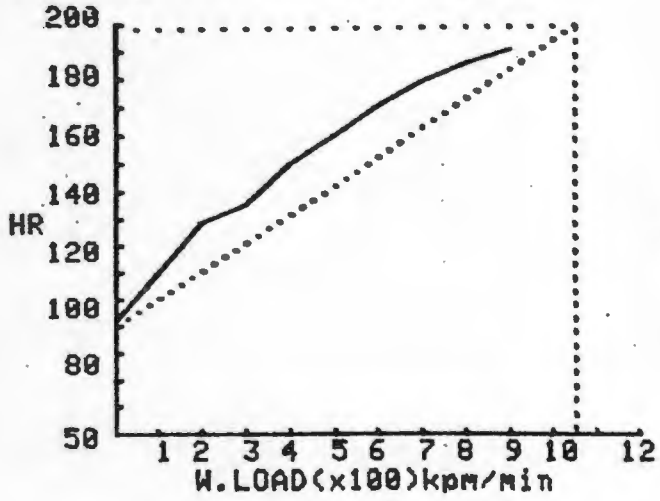
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	88	11	20	554	94	28	110	70
100	110	11	0	0	95	0		
200	135	22	27	827	92	24	130	70
300	150	40	42	945	92	28		
400	160	48	42	1142	91	22	130	70
500	180	55	48	1154	91	22		
600	185	64	50	1285	91	20	130	70

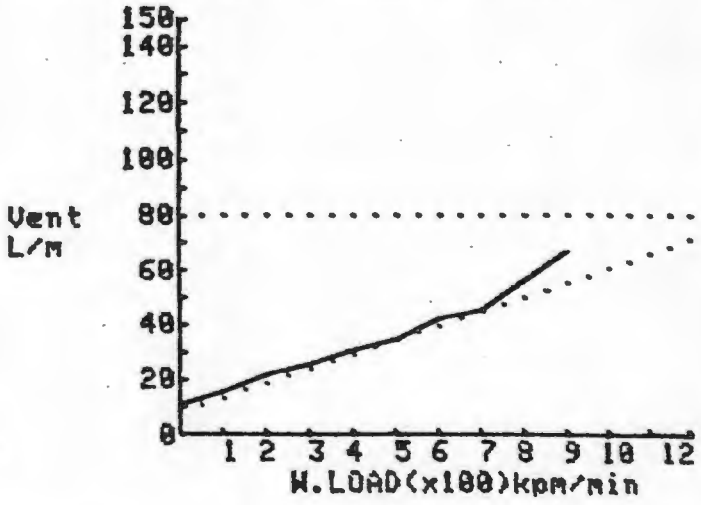
W.LOAD kpm/m	REST	300	0
HEART RATE	88	170	0
VI l/m	11	41	0
Vt ml	554	1110	0
RESP.RATE	20	37	0
VO2 ml/m	263	1102	0
VO2 ml/kg/m	5.2	21.6	0.0
VCO2 ml/m	173	915	0
R	0.66	0.83	0.00
PECO2 mm	14	19	0
PETCO2 mm	28	21	0
PVCO2 mm	44	58	0

W.LOAD kpm/m	REST	300	0
PaCO2 mm	30	34	0
Vd/Vt %	27	29	0
VA l/m	8	29	0
PaO2 mm	91	85	0
SaO2 %	97	97	0
PAO2 mm	108	111	0
A-aDO2 mm	17	26	0
QS/QT %	1	2	0
QT l/m	2.5	8.7	0.0
STR.VOL ml	28	51	0
PH	7.42	7.39	0.00
LACTATE mm/l	0.0	0.0	0.0

PREDICTED VALUES: FEV1: 2960 ml FVC: 3110 ml
Max.HR: 198 Max.W.Load: 1050 kpm/min Max.Vent: 88 L/min

SPIROMETRY:
Pre-exercise: FEV1: 2380 ml FVC: 2700 ml Ratio: 88 %
Lowest post-: FEV1: 2450 ml FVC: 2720 ml Time: 5 min



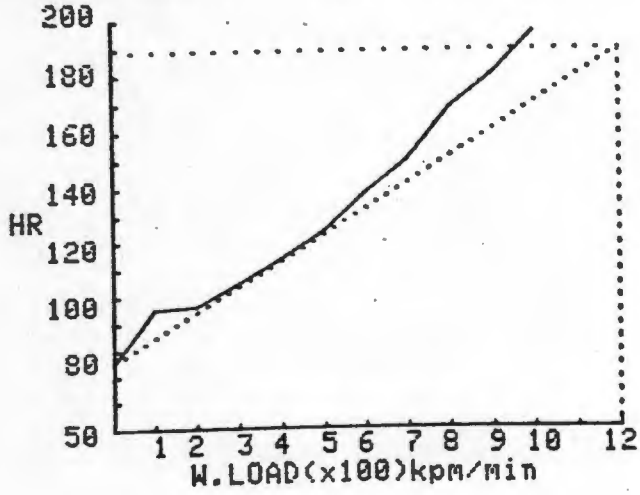


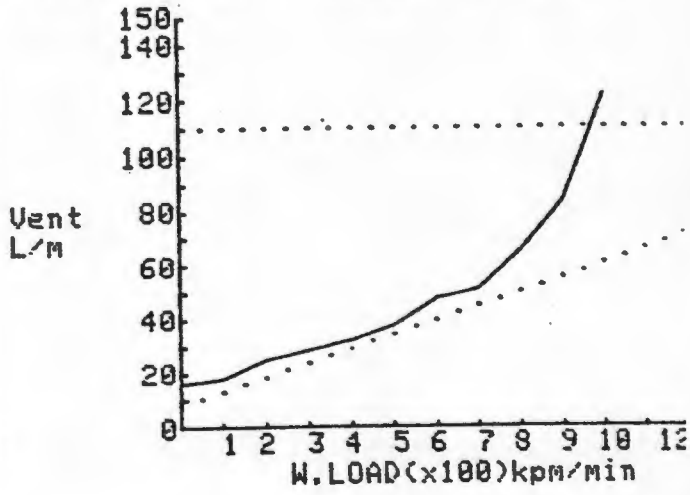
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	92	11	15	702	90	37	110	70
100	110	16	20	785	90	37		
200	129	22	26	844	90	35	120	70
300	135	26	28	913	90	35		
400	150	31	29	1070	89	35	140	70
500	160	35	30	1152	90	35		
600	170	43	32	1331	89	34	160	80
700	179	45	32	1411	88	35		
800	185	56	36	1566	88	32		
900	190	67	44	1527	89	30		

W.LOAD kpm/m	REST	400	550
HEART RATE	92	170	180
VI l/m	11	33	47
Vt ml	702	1207	983
RESP.RATE	15	27	52
VO2 ml/m	256	1042	1435
VO2 ml/kg/m	5.7	23.2	31.9
VCO2 ml/m	241	946	1466
R	0.94	0.91	1.02
PECO2 mm	28	25	27
PETCO2 mm	37	32	32
PVCO2 mm	52	67	75

W.LOAD kpm/m	REST	400	550
PaCO2 mm	39	32	35
Vd/Vt %	28	18	7
VA l/m	8	29	44
PaO2 mm	90	87	95
SaO2 %	97	96	97
PAO2 mm	107	113	114
A-aDO2 mm	17	26	19
QS/QT %	3	2	1
QT l/m	4.4	6.5	9.2
STR.VOL ml	48	38	51
PH	7.39	7.35	7.35
LACTATE mm/l	0.8	0.8	0.8

SPIROMETRY:
Pre-exercise: FEV1: 3080 ml FVC: 4760 ml Ratio: 64 %
Lowest post-: FEV1: 3330 ml FVC: 4770 ml Time: 5 min





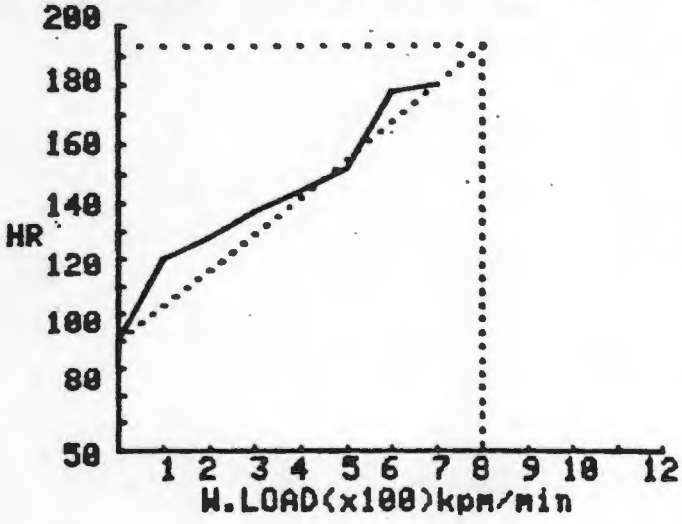
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	75	16	22	722	96	33	110	50
100	95	18	21	841	98	33		
200	96	25	26	970	97	33	120	60
300	105	29	27	1061	97	33		
400	114	32	27	1187	97	33	150	60
500	124	38	28	1343	97	33		
600	138	48	29	1648	98	32		
700	150	51	29	1754	98	31		
800	168	65	35	1866	98	30	170	60
900	180	84	41	2045	99	23		
1000	195	122	57	2145	99	18		

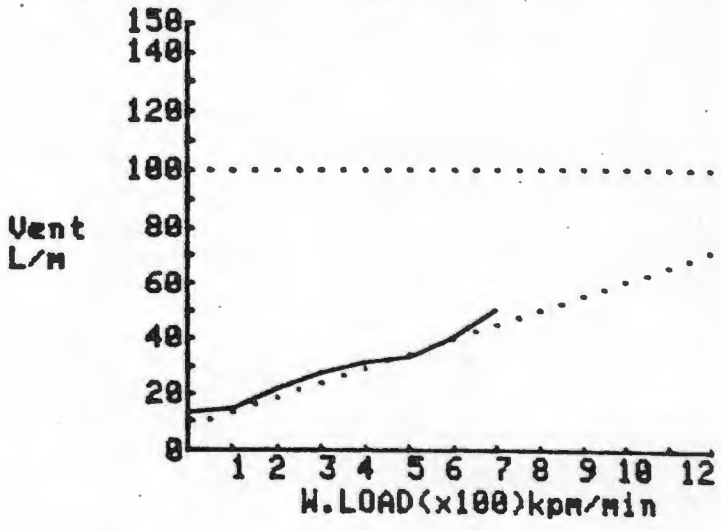
W.LOAD kpm/m	REST	400	600
HEART RATE	75	140	156
VI l/m	16	45	55
Vt ml	722	1437	1783
RESP.RATE	22	31	31
VO2 ml/m	330	1309	1665
VO2 ml/kg/m	5.3	21.1	26.8
VCO2 ml/m	324	1106	1441
R	0.98	0.84	0.87
PECO2 mm	18	22	23
PETCO2 mm	33	27	28
PVCO2 mm	50	57	57

W.LOAD kpm/m	REST	400	600
PaCO2 mm	34	29	27
Vd/Vt %	28	15	8
VA l/m	11	38	51
PaO2 mm	107	110	84
SaO2 %	98	98	96
PAO2 mm	115	117	120
A-aDO2 mm	8	7	36
QS/QT %	1	0	2
QT l/m	4.6	8.5	10.2
STR.VOL ml	61	61	65
PH	7.44	7.33	7.36
LACTATE mm/l	0.0	0.0	0.0

SPIROMETRY:

Pre-exercise:	FEV1: 2740 ml	FVC: 3220 ml	Ratio: 85	%
Lowest post-:	FEV1: 2590 ml	FVC: 3170 ml	Time: 5	min



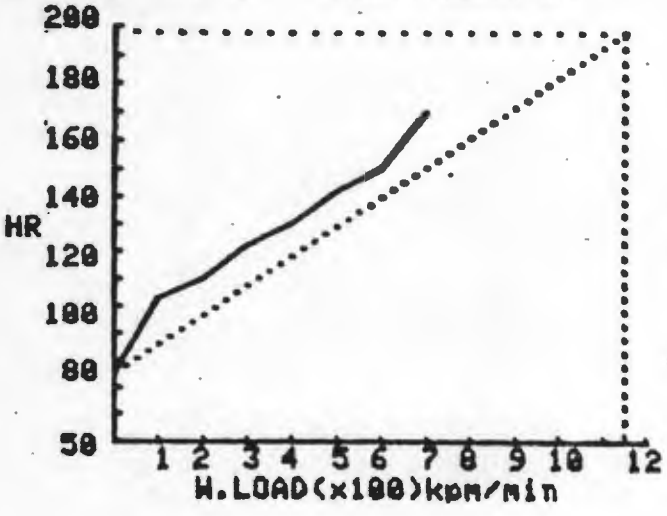


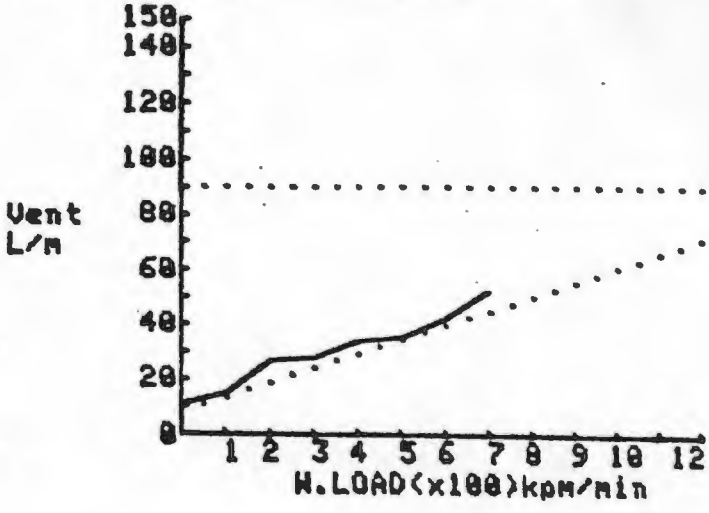
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Diast.
0	90	13	24	536	96	39	120	80
100	120	14	19	758	96	38		
200	128	22	23	948	97	37	140	90
300	137	28	29	950	97	38		
400	144	31	30	1047	96	35	130	100
500	152	33	31	1067	96	38		
600	178	40	30	1342	96	32	130	100
700	180	51	38	1333	96	29		

W.LOAD kpm/m	REST	400	0
HEART RATE	90	160	0
VI l/m	13	46	0
Vt ml	536	1049	0
RESP.RATE	24	44	0
VO2 ml/m	290	1296	0
VO2 ml/kg/m	6.4	28.8	0.0
VCO2 ml/m	226	1327	0
R	0.78	1.02	0.00
PECO2 mm	15	25	0
PETCO2 mm	39	29	0
PVCO2 mm	49	62	0

W.LOAD kpm/m	REST	400	0
PaCO2 mm	37	35	0
Vd/Vt %	31	15	0
VA l/m	9	39	0
PaO2 mm	97	99	0
SaO2 %	98	98	0
PAO2 mm	103	114	0
A-aDO2 mm	6	15	0
QS/QT %	1	1	0
QT l/m	4.2	11.9	0.0
STR.VOL ml	46	74	0
PH	7.41	7.38	0.00
LACTATE mM/l	0.0	0.0	0.0

SPIROMETRY:
Pre-exercise: FEV1: 2690 ml FVC: 3400 ml Ratio: 79 %
Lowest post-: FEV1: 2850 ml FVC: 3690 ml Time: 5 min



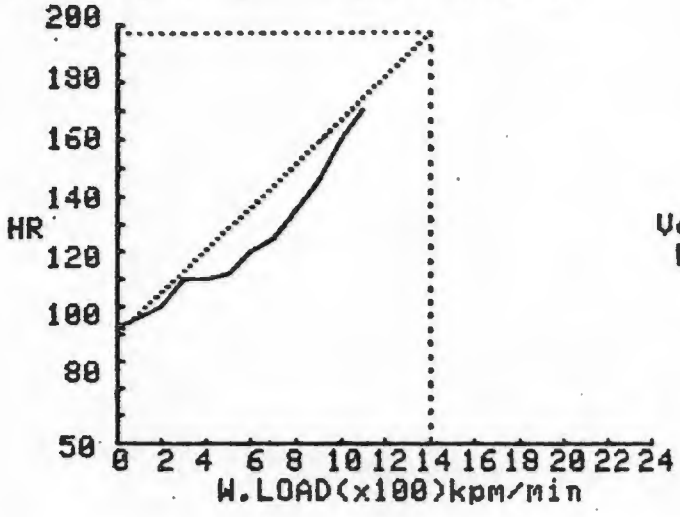


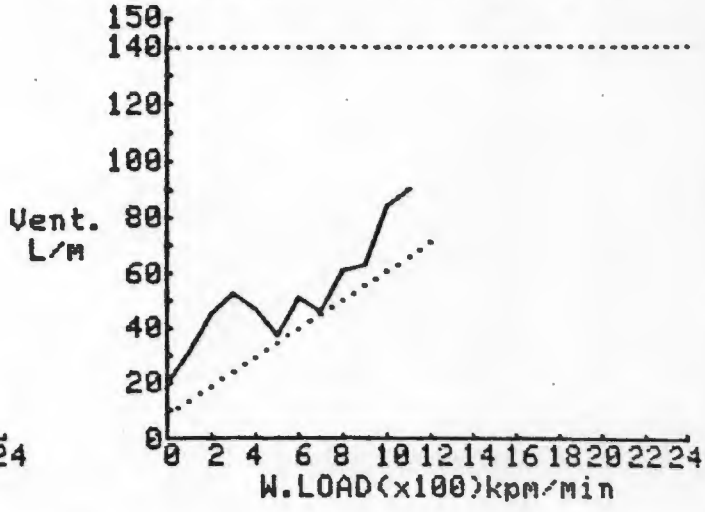
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	75	11	19	568	95	32	130	90
100	103	15	26	562	96	29		
200	110	26	34	776	96	29	160	100
300	122	27	30	909	97	32		
400	130	34	31	1081	96	32	170	90
500	142	35	32	1093	98	31		
600	150	42	35	1209	95	33	170	90
700	170	52	40	1311	96	31		

W.LOAD kpm/m	REST	400	0
HEART RATE	75	143	0
VI l/m	9	43	0
Vt ml	556	1114	0
RESP.RATE	17	39	0
VO2 ml/m	259	1369	0
VO2 ml/kg/m	4.3	22.8	0.0
VCO2 ml/m	187	1239	0
R	0.72	0.91	0.00
PECO2 mm	17	25	0
PETCO2 mm	32	29	0
PVCO2 mm	46	62	0

W.LOAD kpm/m	REST	400	0
PaCO2 mm	36	32	0
Vd/Vt %	26	9	0
VA l/m	7	40	0
PaO2 mm	90	101	0
SaO2 %	97	98	0
PAO2 mm	103	115	0
A-aDO2 mm	13	15	0
QS/QT %	2	1	0
QT l/m	4.3	9.5	0.0
STR.VOL ml	57	67	0
PH	7.39	7.39	0.00
LACTATE mm/l	0.0	0.0	0.0

SPIROMETRY:
Pre-exercise: FEV1: 3910 ml FVC: 4780 ml Ratio: 81 %
Lowest post-: FEV1: 4130 ml FVC: 4940 ml Time: 5 min





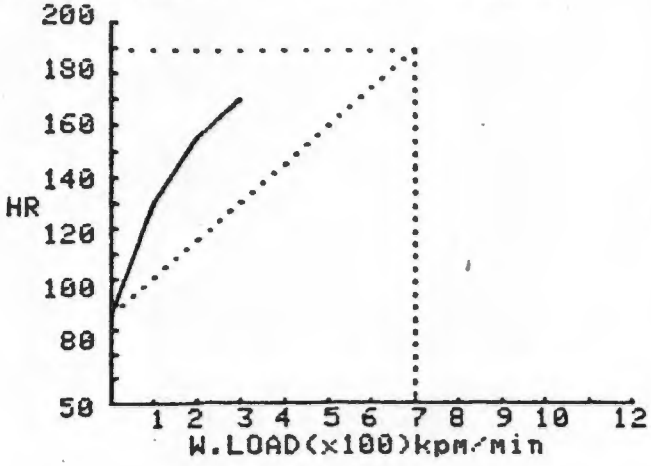
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	93	19	25	767	97	26		
100	96	31	22	1426	98	22	110	70
200	100	45	30	1510	97	21		
300	110	52	35	1497	97	23	110	70
400	110	47	32	1460	98	24		
500	112	37	29	1277	97	28	125	70
600	120	51	31	1650	97	27		
700	125	46	30	1523	97	31	150	80
800	135	61	35	1751	97	30		
900	145	63	34	1851	97	30	160	80
1000	160	84	45	1873	97	31		
1100	170	90	48	1884	97	26		

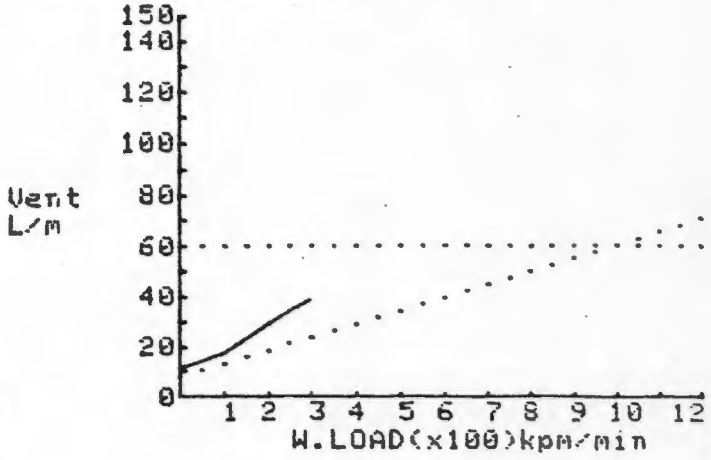
W.LOAD kpm/m	REST	700	0
HEART RATE	94	140	0
VI l/m	22	56	0
Vt ml	841	2013	0
RESP.RATE	26	28	0
VO2 ml/m	284	1671	0
VO2 ml/kg/m	4.6	27.0	0.0
VCO2 ml/m	345	1798	0
R	1.21	1.08	0.00
PECO2 mm	14	27	0
PETCO2 mm	21	35	0
PVCO2 mm	37	65	0

W.LOAD kpm/m	REST	700	0
PaCO2 mm	28	32	0
Vd/Vt %	33	7	0
VA l/m	15	52	0
PaO2 mm	111	102	0
SaO2 %	98	98	0
PAO2 mm	125	119	0
A-aDO2 mm	14	17	0
QS/QT %	1	1	0
QT l/m	68	125	0.0
STR.VOL ml	72	87	0
PH	7.53	7.42	0.00
LACTATE mm/l	0.0	0.0	0.0

PREDICTED VALUES: FEV1: 1810 ml FVC: 2230 ml
Max.HR: 189 Max.W.Load: 700 kpm/min Max.Vent: 60 L/min

SPIROMETRY:
Pre-exercise: FEV1: 1750 ml FVC: 2090 ml Ratio: 83 %
Lowest post-: FEV1: 1820 ml FVC: 2130 ml Time: 5 min



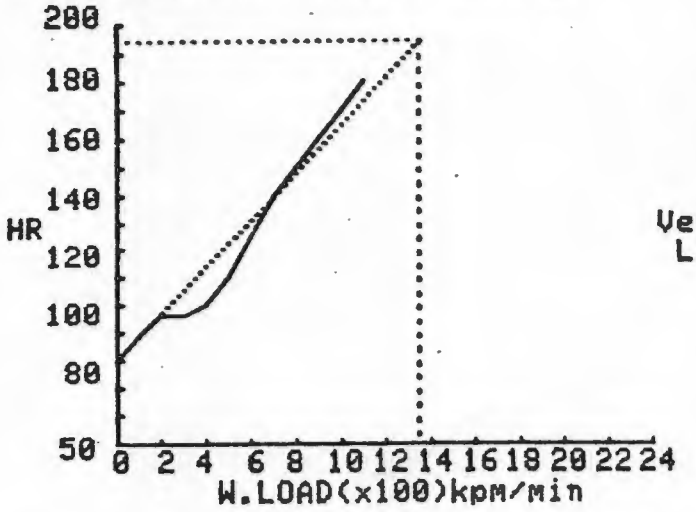


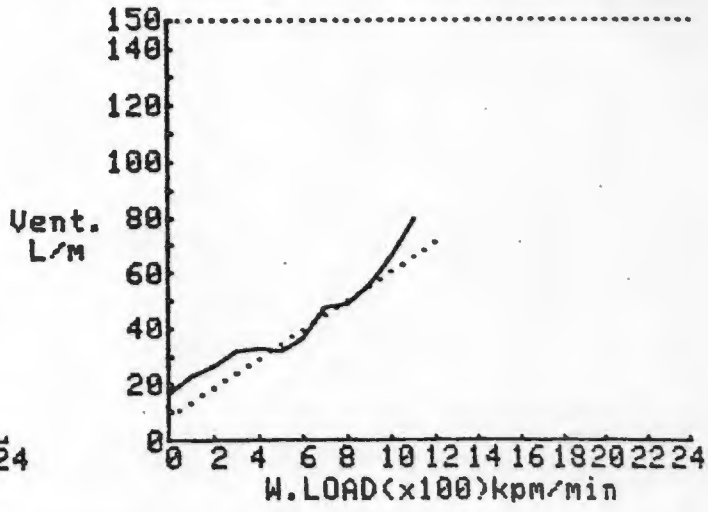
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	86	11	23	490	94	25	120	70
100	130	18	24	730	94	25		
200	155	29	35	837	94	22	120	70
300	170	39	41	951	94	20		

W.LOAD kpm/m	REST	100	0
HEART RATE	86	150	0
VI l/m	9	32	0
Vt ml	497	998	0
RESP.RATE	19	32	0
VO2 ml/m	195	726	0
VO2 ml/kg/m	4.5	16.9	0.0
VCO2 ml/m	148	631	0
R	0.76	0.87	0.00
PECO2 mm	14	17	0
PETCO2 mm	25	24	0
PVCO2 mm			0

W.LOAD kpm/m	REST	100	0
PaCO2 mm	28	32	0
Vd/Vt %	20	32	0
VA l/m	7	22	0
PaO2 mm	91	77	0
SaO2 %	97	95	0
PAO2 mm	114	113	0
A-aDO2 mm	23	37	0
QS/QT %	1	7	0
QT l/m	5.71	11.30	0.0
STR.VOL ml	66	75	0
PH	7.43	7.39	0.00
LACTATE mm/l	1.5	3.2	0.0

SPIROMETRY:
Pre-exercise: FEV1: 4200 ml FVC: 4850 ml Ratio: 86 %
Lowest post-: FEV1: 4470 ml FVC: 5020 ml Time: 5 min



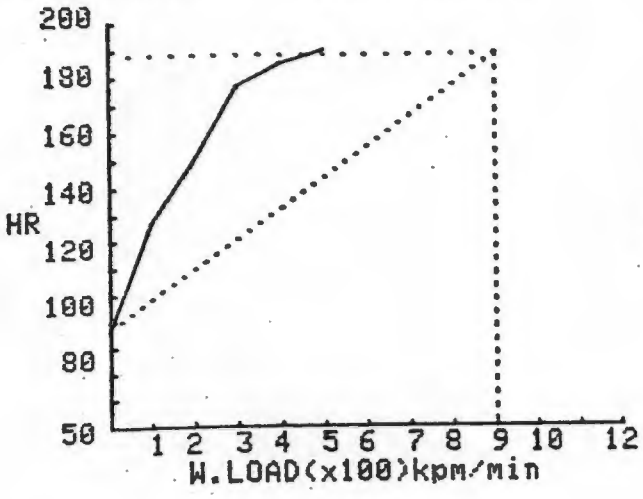


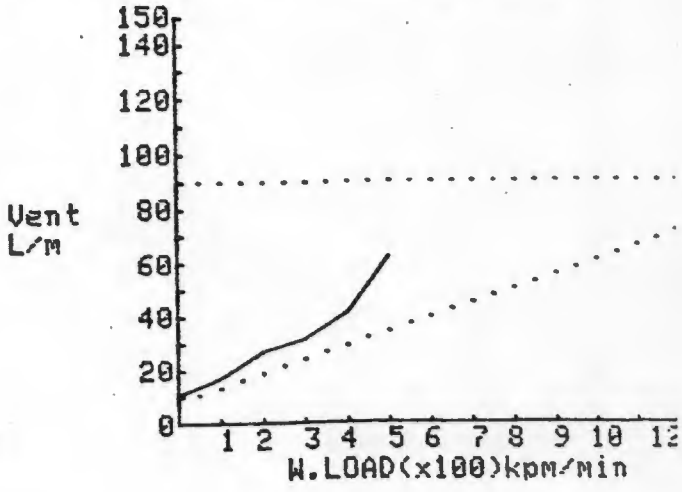
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	80	16	9	1803	96	22	130	80
100	89	23	12	1909	97	25		
200	96	27	12	2210	97	25	140	80
300	96	32	13	2441	97	26		
400	100	33	17	1927	98	30	160	100
500	110	32	15	2131	97	31		
600	125	37	17	2153	96	34	160	110
700	140	47	22	2157	96	33		
800	150	49	23	2128	96	32	190	110
900	160	56	32	1748	96	30		
1000	170	66	36	1832	96	28	190	120
1100	180	80	41	1942	96	25		

W.LOAD kpm/m	REST	500	0
HEART RATE	88	120	0
VI l/m	13	42	0
Vt ml	1670	1767	0
RESP.RATE	8	24	0
VO2 ml/m	306	1758	0
VO2 ml/kg/m	5.0	28.6	0.0
VCO2 ml/m	266	1324	0
R	0.87	0.75	0.00
PECO2 mm	17	27	0
PETCO2 mm	22	36	0
PVCO2 mm	34	57	0

W.LOAD kpm/m	REST	500	0
PaCO2 mm	26	34	0
Vd/Vt %	23	10	0
VA l/m	10	38	0
PaO2 mm	101	63	0
SaO2 %	98	92	0
PAO2 mm	122	108	0
A-aDO2 mm	20	45	0
QS/QT %	1	8	0
QT l/m	5.3	12.7	0.0
STR.VOL ml	60	106	0
PH	7.54	7.41	0.00
LACTATE mm/l	0.0	0.0	0.0

SPIROMETRY:
Pre-exercise: FEV1: 2620 ml FVC: 2840 ml Ratio: 92 %
Lowest post-: FEV1: 2670 ml FVC: 2730 ml Time: 5 min



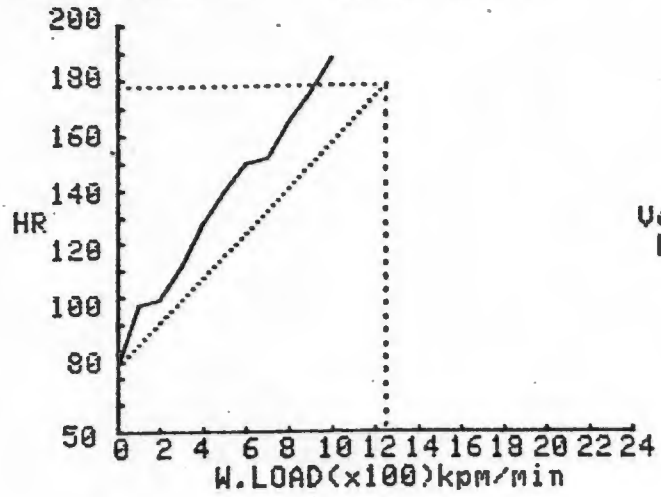


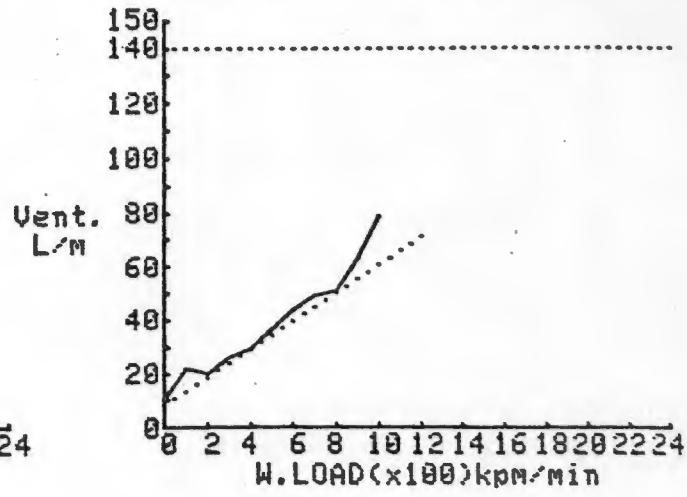
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	87	11	19	565	97	33	110	70
100	127	17	27	631	97	29		
200	150	27	28	966	97	30	120	70
300	177	31	26	1207	97	30		
400	185	41	31	1332	97	27	140	70
500	190	63	47	1335	96	22		

W.LOAD kpm/m	REST	300	0
HEART RATE	87	170	0
VI l/m	11	38	0
Vt ml	673	1089	0
RESP.RATE	17	35	0
VO2 ml/m	269	923	0
VO2 ml/kg/m	4.6	15.6	0.0
VCO2 ml/m	206	909	0
R	0.76	0.98	0.00
PECO2 mm	16	21	0
PETCO2 mm	33	27	0
PVCO2 mm	47	55	0

W.LOAD kpm/m	REST	300	0
PaCO2 mm	33	28	0
Vd/Vt %	30	13	0
VA l/m	8	33	0
PaO2 mm	95	104	0
SaO2 %	98	98	0
PAO2 mm	108	120	0
A-aDO2 mm	13	16	0
QS/QT %	1	1	0
QT l/m	3.1	7.3	0.0
STR.VOL ml	36	43	0
PH	7.42	7.34	0.00
LACTATE mm/l	0.0	0.0	0.0

SPIROMETRY:
Pre-exercise: FEV1: 4020 ml FVC: 4940 ml Ratio: 81 %
Lowest post-: FEV1: 4200 ml FVC: 5110 ml Time: 5 min





W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	74	10	11	924	98	37	170	95
100	97	22	12	1824	99	38		
200	99	20	13	1516	99	40	200	100
300	112	26	14	1846	99	42		
400	128	29	16	1824	99	41	110	95
500	140	37	16	2292	99	43		
600	150	44	16	2736	99	42	220	100
700	152	49	18	2736	99	39		
800	165	51	19	2676	98	40	220	100
900	175	63	24	2627	99	34		
1000	188	79	29	2718	98	30	230	100

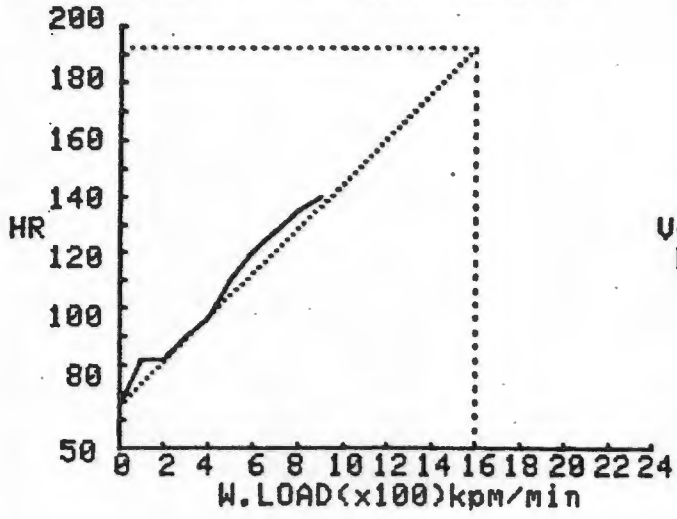
W.LOAD kpm/m	REST	500	0
HEART RATE	92	147	0
VI l/m	12	49	0
Vt ml	1231	2141	0
RESP.RATE	10	23	0
VO2 ml/m	372	1518	0
VO2 ml/kg/m	3.7	15.2	0.0
VCO2 ml/m	273	1652	0
R	0.73	1.09	0.00
PECO2 mm	19	29	0
PETCO2 mm	33	33	0
PVCO2 mm	44	62	0

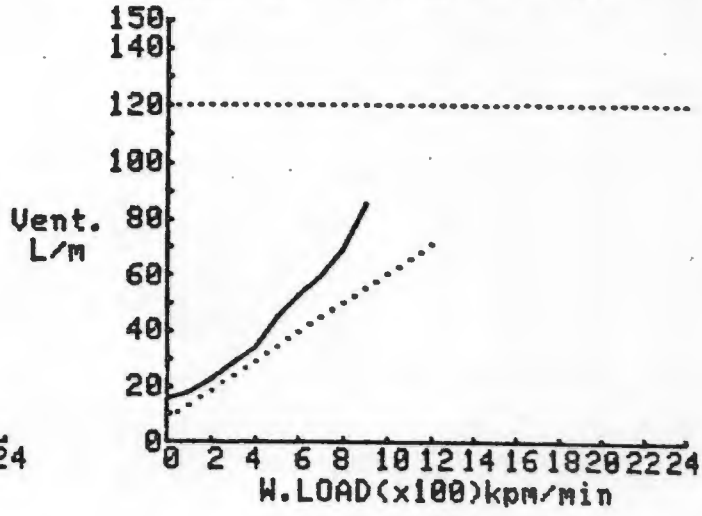
W.LOAD kpm/m	REST	500	0
PaCO2 mm	33	38	0
Vd/Vt %	30	18	0
VA l/m	9	41	0
PaO2 mm	90	90	0
SaO2 %	97	97	0
PAO2 mm	104	112	0
A-aDO2 mm	14	22	0
QS/QT %	2	2	0
QT l/m	5.4	16.6	0.0
STR.VOL ml	59	113	0
PH	7.42	7.38	0.00
LACTATE mm/l	0.0	0.0	0.0

SPIROMETRY:

Pre-exercise: FEV1: 3490 ml FVC: 4640 ml Ratio: 75 %

Lowest post-: FEV1: 3600 ml FVC: 4580 ml Time: 5 min





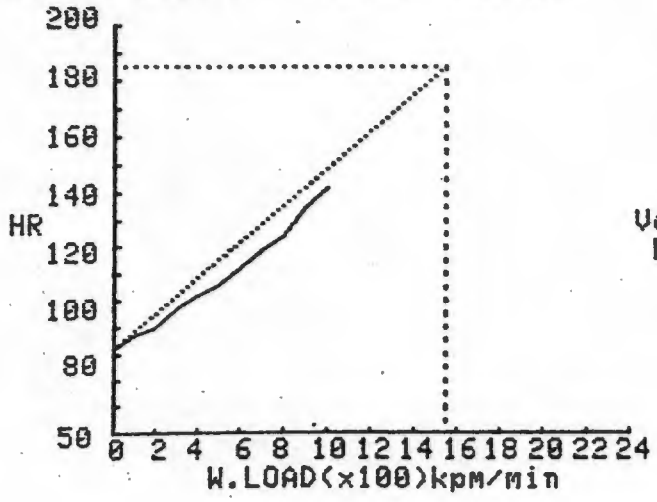
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	65	15	18	853	47	23	110	80
100	82	18	18	993	97	28		
200	82	23	19	1189	97	29	130	90
300	90	29	20	1432	97	32		
400	96	34	22	1561	97	31	142	80
500	110	45	25	1787	97	32		
600	120	53	28	1883	97	29	150	90
700	128	60	27	2206	98	28		
800	135	70	33	2113	98	26	170	80
900	140	86	36	2375	98	23		

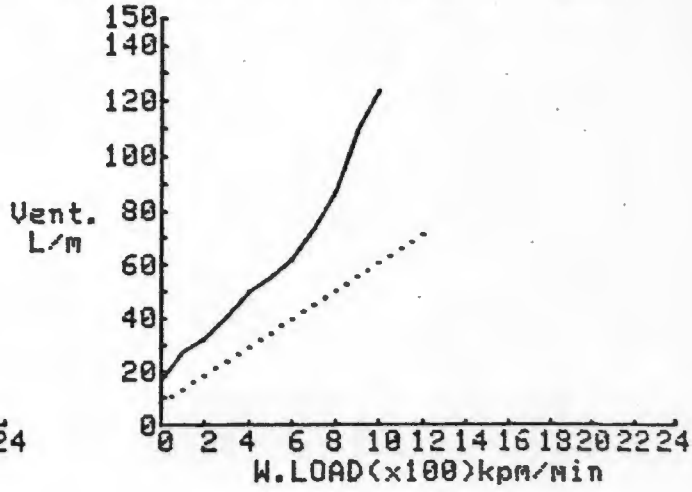
W.LOAD kpm/m	REST	450	0
HEART RATE	60	125	0
VI l/m	12	47	0
Vt ml	693	1878	0
RESP.RATE	17	25	0
VO2 ml/m	233	1240	0
VO2 ml/kg/m	3.1	16.3	0.0
VCO2 ml/m	260	1470	0
R	1.11	1.19	0.00
PECO2 mm	19	27	0
PETCO2 mm	28	33	0
PVCO2 mm	46	53	0

W.LOAD kpm/m	REST	450	0
PaCO2 mm	32	31	0
Vd/Vt %	19	5	0
VA l/m	10	45	0
PaO2 mm	101	110	0
SaO2 %	98	98	0
PAO2 mm	120	123	0
A-aDO2 mm	19	13	0
QS/QT %	1	1	0
QT l/m	3.8	14.5	0.0
STR.VOL ml	64	116	0
PH	7.45	7.39	0.00
LACTATE mm/l	0.0	0.0	0.0

SPIROMETRY:

Pre-exercise:	FEV1: 4590 ml	FVC: 5280 ml	Ratio: 86	%
Lowest post-:	FEV1: 4360 ml	FVC: 5350 ml	Time: 5	min





W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	82	17	18	922	92	25	110	80
100	87	28	18	1537	92	25		
200	90	32	22	1462	91	24	120	80
300	97	40	18	2240	90	25		
400	102	50	22	2277	89	24	130	80
500	106	55	21	2641	88	24		
600	112	62	24	2593	88	23	140	80
700	119	73	23	3168	88	24		
800	124	88	29	3023	88	22	170	90
900	134	109	36	3027	88	21		
1000	142	123	41	3012	88	18	190	100

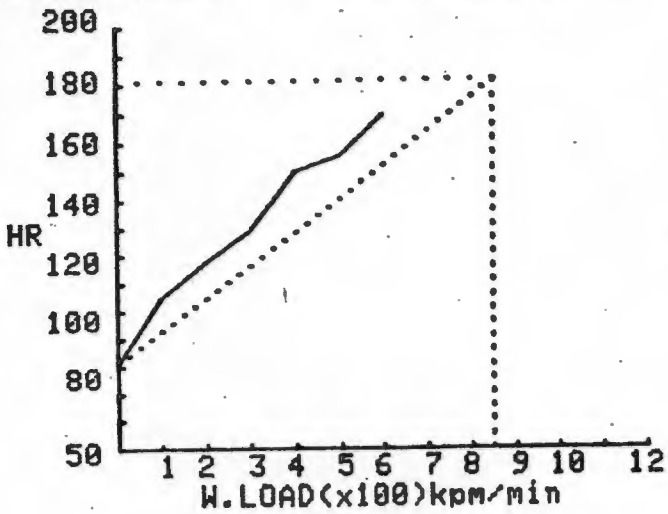
W.LOAD kpm/m	REST	500	0
HEART RATE	78	113	0
VI l/m	14	72	0
Vt ml	1109	2683	0
RESP.RATE	13	27	0
VO2 ml/m	331	1560	0
VO2 ml/kg/m	3.6	17.1	0.0
VCO2 ml/m	265	1458	0
R	0.80	0.93	0.00
PECO2 mm	16	17	0
PETCO2 mm	25	22	0
PVCO2 mm	35	43	0

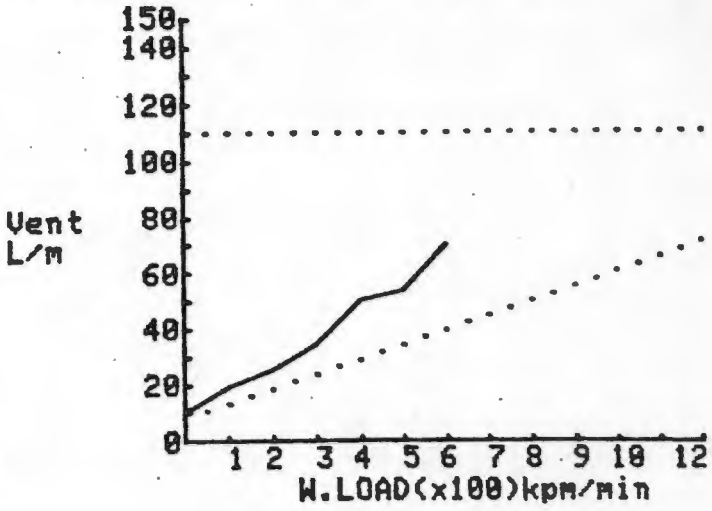
W.LOAD kpm/m	REST	500	0
PaCO2 mm	30	26	0
Vd/Vt %	33	27	0
VA l/m	10	53	0
PaO2 mm	73	61	0
SaO2 %	95	92	0
PAO2 mm	113	121	0
A-aDO2 mm	40	60	0
QS/QT %	11	9	0
QT l/m	9.7	16.4	0.0
STR.VOL ml	125	145	0
PH	7.42	7.40	0.00
LACTATE mm/l	0.0	0.0	0.0

SPIROMETRY:

Pre-exercise: FEV1: 3100 ml FVC: 3780 ml Ratio: 82 %

Lowest post-: FEV1: 3220 ml FVC: 3850 ml Time: 6 min





W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	81	18	15	676	97	32	130	90
100	105	19	21	909	97	30		
200	118	26	21	1227	97	33	150	100
300	129	35	26	1328	97	30		
400	150	51	33	1537	97	29	170	110
500	155	54	30	1803	97	27		
600	169	71	39	1809	97	23		

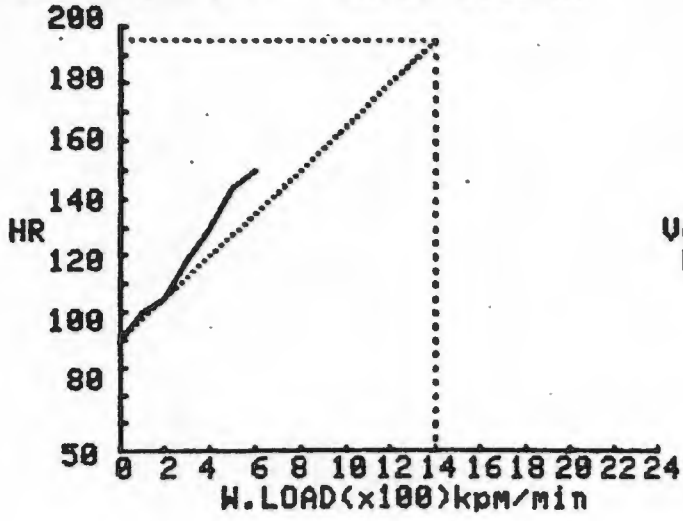
W.LOAD kpm/m	REST	300	0
HEART RATE	81	129	0
VI l/m	9	34	0
Vt ml	764	1482	0
RESP.RATE	12	23	0
VO2 ml/m	235	1038	0
VO2 ml/kg/m	3.9	17.3	0.0
VCO2 ml/m	174	829	0
R	0.74	0.80	0.00
PECO2 mm	16	21	0
PETCO2 mm	32	29	0
PVCO2 mm	42	51	0

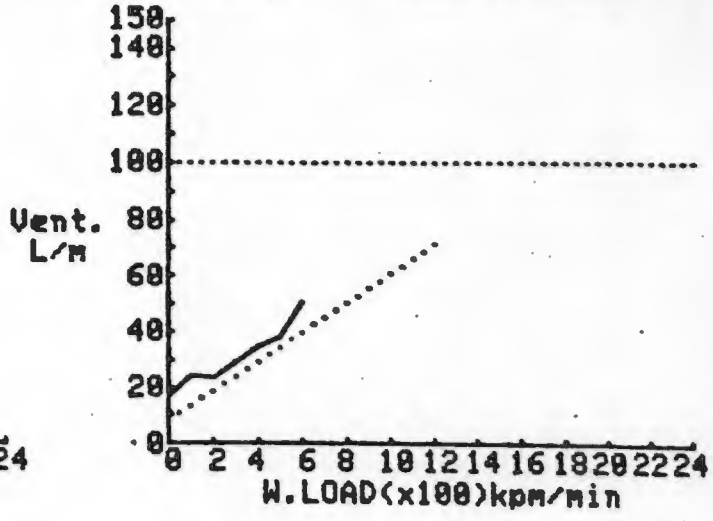
W.LOAD kpm/m	REST	300	0
PaCO2 mm	35	31	0
Vd/Vt %	34	21	0
VA l/m	6	27	0
PaO2 mm	93	98	0
SaO2 %	97	98	0
PAO2 mm	105	113	0
A-aDO2 mm	12	15	0
QS/QT %	3	1	0
QT l/m	5.5	8.7	0.0
STR.VOL ml	68	68	0
PH	7.42	7.41	0.00
LACTATE mm/l	0.0	0.0	0.0

SPIROMETRY:

Pre-exercise: FEV1: 2940 ml FVC: 3630 ml Ratio: 80 %

Lowest post-: FEV1: 3010 ml FVC: 3730 ml Time: 6 min



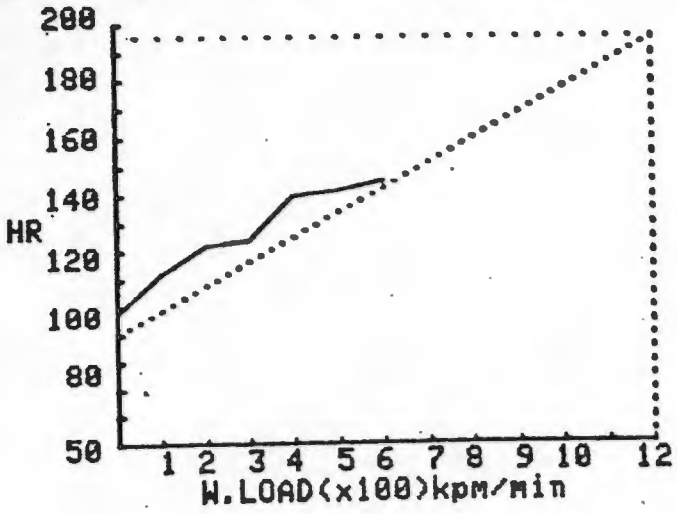


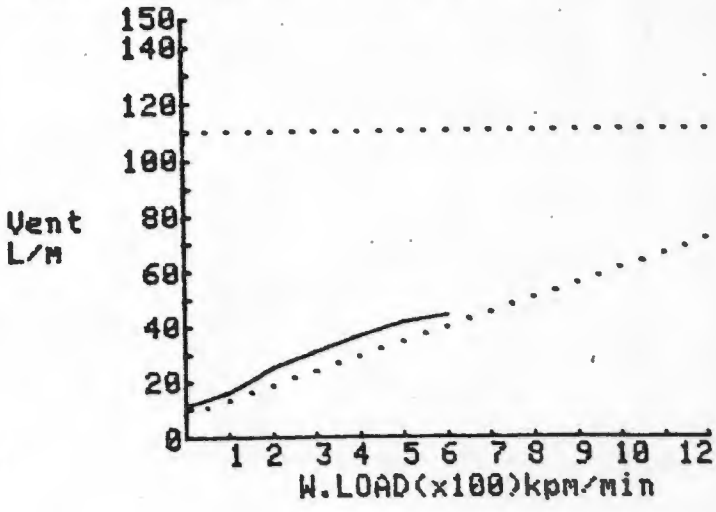
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	90	17	27	611	95	31	120	70
100	100	24	32	754	95	33		
200	105	23	28	824	94	33	140	80
300	119	29	28	1037	94	34		
400	130	35	33	1056	94	34	140	80
500	144	38	33	1159	94	34		
600	150	51	34	1488	94	32	140	80

W.LOAD kpm/m	REST	300	0
HEART RATE	90	124	0
VI l/m	17	31	0
Vt ml	611	1045	0
RESP.RATE	27	30	0
VO2 ml/m	353	944	0
VO2 ml/kg/m	5.6	15.0	0.0
VCO2 ml/m	304	835	0
R	0.86	0.88	0.00
PECO2 mm	16	23	0
PETCO2 mm	31	32	0
PVCO2 mm	46	52	0

W.LOAD kpm/m	REST	300	0
PaCO2 mm	36	35	0
Vd/Vt %	31	20	0
VA l/m	11	25	0
PaO2 mm	90	91	0
SaO2 %	97	97	0
PAO2 mm	108	110	0
A-aDO2 mm	18	18	0
QS/QT %	3	2	0
QT l/m	6.5	11.3	0.0
STR.VOL ml	72	91	0
PH	7.41	7.37	0.00
LACTATE mm/l	0.0	0.0	0.0

SPIROMETRY:
Pre-exercise: FEV1: 3250 ml FVC: 3880 ml Ratio: 83 %
Lowest post-: FEV1: 3350 ml FVC: 3750 ml Time: 5 min





W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	98	11	21	529	94	29	110	60
100	112	16	14	1151	93	36		
200	122	25	26	964	93	36	130	70
300	124	31	29	1067	93	37		
400	140	37	24	1530	93	35	150	70
500	142	42	31	1340	93	34		
600	145	44	33	1329	93	33		

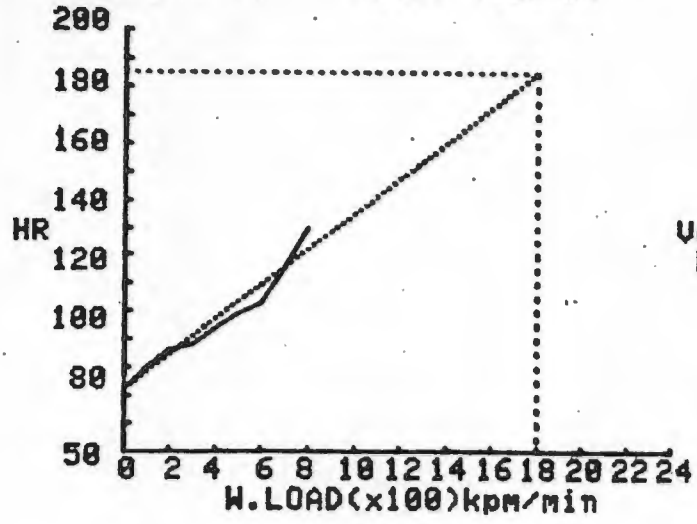
W.LOAD kpm/m	REST	250	0
HEART RATE	98	127	0
VI l/m	11	34	0
Vt ml	529	1183	0
RESP.RATE	21	29	0
VO2 ml/m	235	1025	0
VO2 ml/kg/m	4.3	18.8	0.0
VCO2 ml/m	178	994	0
R	0.76	0.97	0.00
PECO2 mm	14	25	0
PETCO2 mm	29	31	0
PVCO2 mm	43	53	0

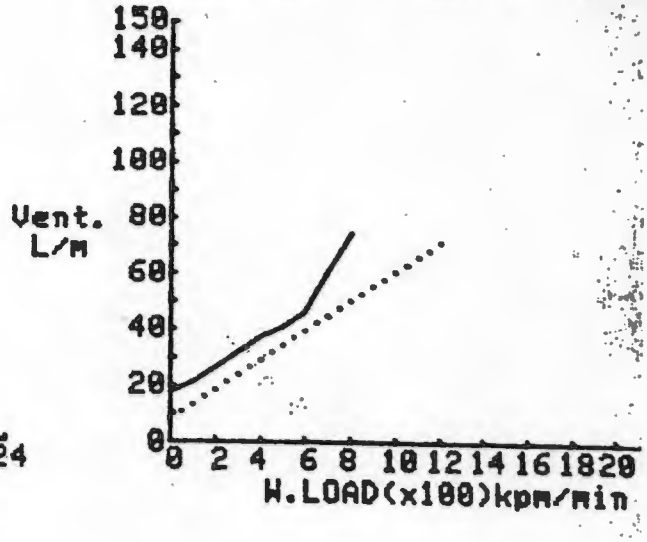
W.LOAD kpm/m	REST	250	0
PaCO2 mm	37	35	0
Vd/Vt %	34	16	0
VA l/m	7	29	0
PaO2 mm	93	101	0
SaO2 %	97	98	0
PAO2 mm	104	114	0
A-aDO2 mm	11	13	0
QS/QT %	2	1	0
QT l/m	6.3	12.6	0.0
STR.VOL ml	64	100	0
PH	7.43	7.41	0.00
LACTATE mm/l	0.0	0.0	0.0

SPIROMETRY:

Pre-exercise: FEV1: 4450 ml FVC: 5150 ml Ratio: 86 %

Lowest post-: FEV1: 4460 ml FVC: 5230 ml Time: 5 min





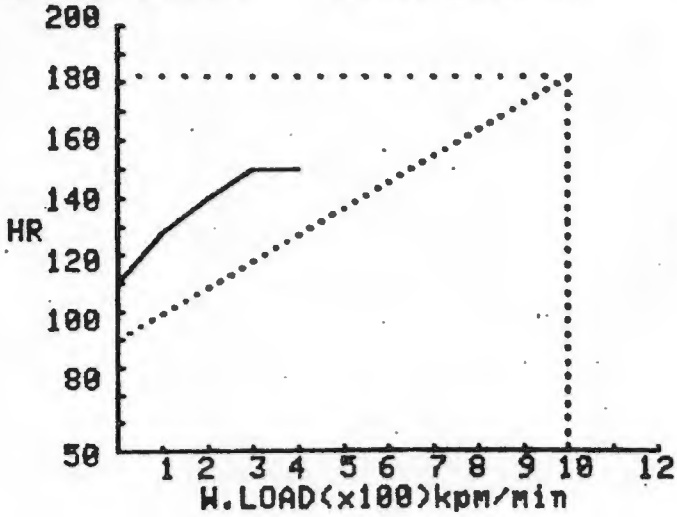
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	72	17	18	957	94	33	110	70
100	80	21	16	1315	94	34		
200	86	27	20	1332	94	34	130	80
300	88	32	20	1586	94	35		
400	94	38	24	1563	94	35	130	80
500	99	41	26	1573	95	36	140	80
600	103	46	28	1653	96	36		
700	116	61	33	1838	96	34	150	90
800	130	74	34	2185	96	35		

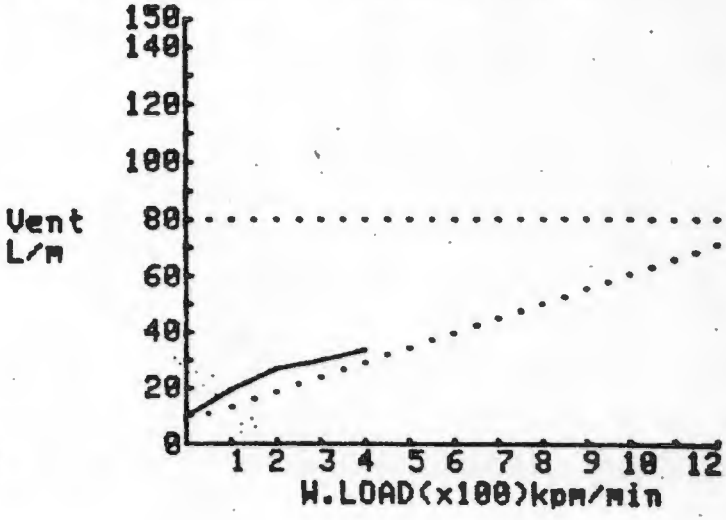
W.LOAD kpm/m	REST	350	0
HEART RATE	72	98	0
VI l/m	17	42	0
Vt ml	957	1631	0
RESP.RATE	18	26	0
VO2 ml/m	487	1141	0
VO2 ml/kg/m	4.6	10.8	0.0
VCO2 ml/m	356	1147	0
R	0.73	1.01	0.00
PECO2 mm	18	23	0
PETCO2 mm	33	28	0
PVCO2 mm	45	61	0

W.LOAD kpm/m	REST	350	0
PaCO2 mm	33	35	0
Vd/Vt %	30	24	0
VA l/m	12	32	0
PaO2 mm	98	88	0
SaO2 %	98	97	0
PAO2 mm	106	113	0
A-aDO2 mm	8	26	0
QS/QT %	1	2	0
QT l/m	6.0	10.3	0.0
STR.VOL ml	83	105	0
PH	7.45	7.39	0.00
LACTATE mm/l	0.0	0.0	0.0

SPIROMETRY:

Pre-exercise:	FEV1: 2170 ml	FVC: 2530 ml	Ratio: 85	%
Lowest post-:	FEV1: 2170 ml	FVC: 2490 ml	Time: 5	min



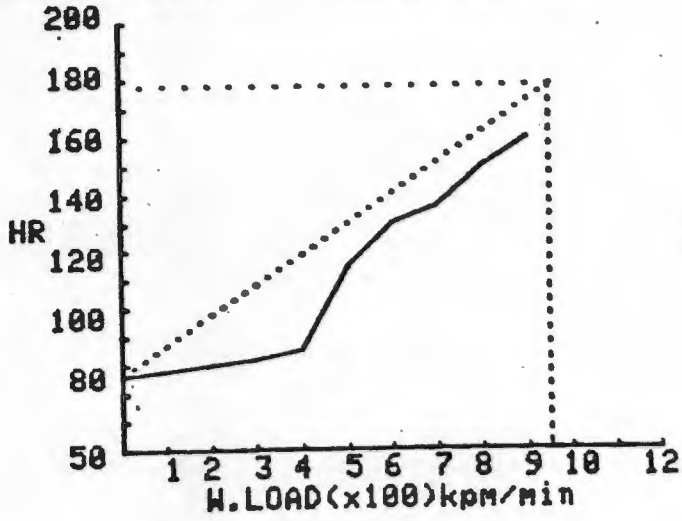


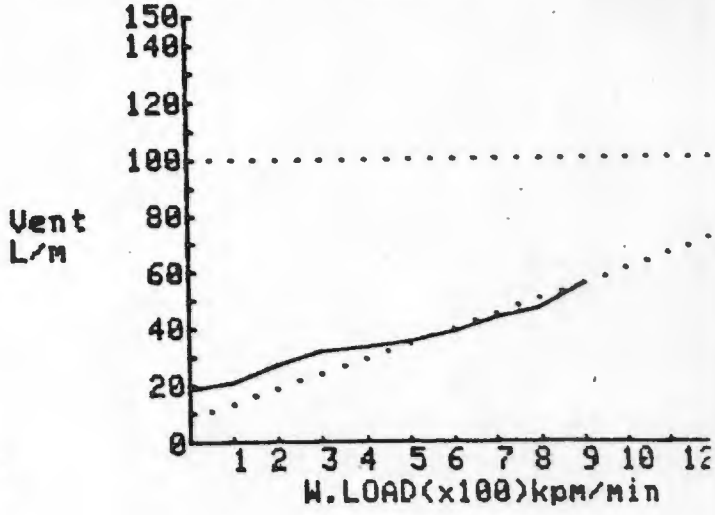
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	110	9	14	678	94	35	150	90
100	128	19	25	764	94	34		
200	140	27	31	871	93	31	170	100
300	150	30	34	886	93	32		
400	150	34	35	962	93	30		

W.LOAD kpm/m	REST	150	0
HEART RATE	110	140	0
VI l/m	10	29	0
Vt ml	688	903	0
RESP.RATE	14	32	0
VO2 ml/m	224	1032	0
VO2 ml/kg/m	3.2	14.5	0.0
VCO2 ml/m	180	726	0
R	0.80	0.70	0.00
PECO2 mm	16	22	0
PETCO2 mm	35	31	0
PVCO2 mm	45	52	0

W.LOAD kpm/m	REST	150	0
PaCO2 mm	38	40	0
Vd/Vt %	35	28	0
VA l/m	6	21	0
PaO2 mm	83	81	0
SaO2 %	96	96	0
PAO2 mm	103	95	0
A-aDO2 mm	21	14	0
QS/QT %	6	3	0
QT l/m	4.9	13.5	0.0
STR.VOL ml	45	96	0
PH	7.40	7.39	0.00
LACTATE mm/l	0.0	0.0	0.0

SPIROMETRY:
Pre-exercise: FEV1: 2960 ml FVC: 3670 ml Ratio: 80 %
Lowest post-: FEV1: 3130 ml FVC: 3510 ml Time: 5 min



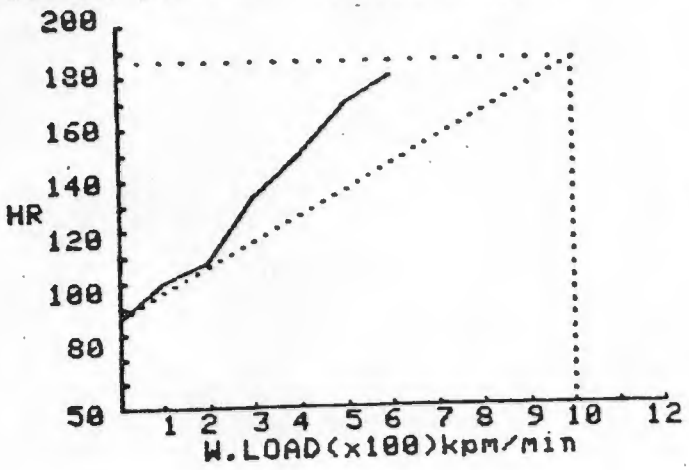


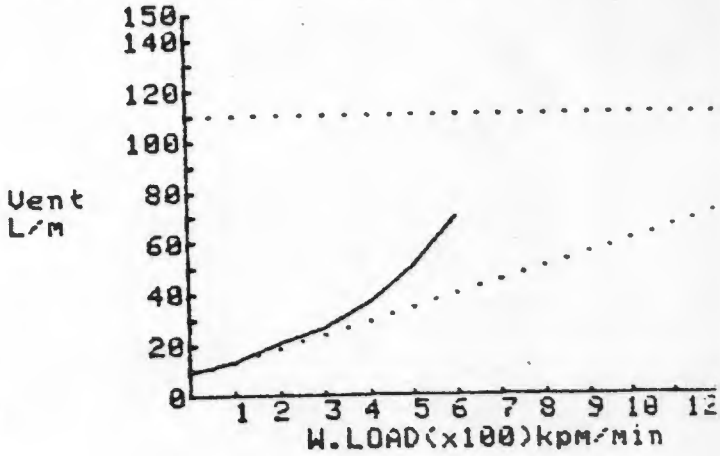
W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	76	19	21	881	94	30	120	80
100	78	21	25	837	97	30		
200	80	27	24	1120	96	32	130	85
300	82	32	26	1229	97	32		
400	85	33	25	1327	97	31	130	80
500	115	35	25	1410	97	31		
600	130	38	26	1475	95	32	130	80
700	136	43	29	1497	94	39		
800	150	47	28	1668	94	38	140	70
900	160	55	29	1900	95	31		

W.LOAD kpm/m	REST	450	0
HEART RATE	56	144	0
VI l/m	15	47	0
Vt ml	688	1583	0
RESP.RATE	22	30	0
VO2 ml/m	363	1560	0
VO2 ml/kg/m	5.7	24.6	0.0
VCO2 ml/m	279	1102	0
R	0.77	0.71	0.00
PECO2 mm	16	20	0
PETCO2 mm	29	28	0
PVCO2 mm	45	62	0

W.LOAD kpm/m	REST	450	0
PaCO2 mm	39	40	0
Vd/Vt %	37	40	0
VA l/m	9	29	0
PaO2 mm	105	80	0
SaO2 %	98	94	0
PAO2 mm	100	96	0
A-aDO2 mm	o	16	0
QS/QT %	o	4	0
QT l/m	10.4	12.3	0.0
STR.VOL ml	185	85	0
PH	7.41	7.26	0.00
LACTATE mm/l	0.0	0.0	0.0

SPIROMETRY:
Pre-exercise: FEV1: 3190 ml FVC: 4040 ml Ratio: 78 %
Lowest post-: FEV1: 3120 ml FVC: 3990 ml Time: 5 min





W.LOAD kpm/m	HEART RATE	VENT. L/m	RESP. RATE	Vt ml	SaO2 %	PetCO2 mmHg	BP Syst.	BP Dias.
0	86	9	13	707	94	31	110	70
100	100	14	25	550	95	27		
200	109	21	19	1095	94	28	120	80
300	133	26	22	1198	93	27		
400	150	37	27	1358	93	24	150	90
500	170	51	34	1486	94	20		
600	180	70	45	1556	92	17		

W.LOAD kpm/m	REST	200	0
HEART RATE	86	113	0
VI l/m	9	27	0
Vt ml	707	1072	0
RESP.RATE	13	25	0
VO2 ml/m	235	669	0
VO2 ml/kg/m	3.7	10.4	0.0
VCO2 ml/m	165	561	0
R	0.70	0.84	0.00
PECO2 mm	16	18	0
PETCO2 mm	31	26	0
PVCO2 mm	44	46	0
$P\bar{v}_{CO_2}$ / $P\bar{v}_{O_2}$ measured	37 / 40	40 / 30	

W.LOAD kpm/m	REST	200	0
PaCO2 mm	34	38	0
Vd/Vt %	33	25	0
VA l/m	6	28	0
PaO2 mm	83	76	0
SaO2 %	97	96	0
PAO2 mm	103	114	0
A-aDO2 mm	20	38	0
QS/QT %	3	4	0
QT l/m	3.6	7.2	0.0
STR.VOL ml	74	90	0
PH	7.45	7.46	0.00
LACTATE mm/l	0.0	0.0	0.0